# Prenyl Rearrangements on Indole Alkaloids from the Marine Bryozoan *Flustra foliacea*: Synthesis of Flustramine A and Studies Towards *ent*-Flustramine C and Debromoflustramine E

Von der Fakultät für Lebenswissenschaften

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(Dr. rer. nat.)

genehmigte

D i s s e r t a t i o n

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### Publikationen

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T. Lindel, N. Marsch, S. K. Adla, "Indole Prenylation in Alkaloid Synthesis", *Top. Curr. Chem.* **2012**, *309*, 67-130.

### Tagungsbeiträge

S. K. Adla, T. Lindel, "Biomimetic Synthesis of Flustramines" (Vortrag). Kolloquium Organische Chemie, Tag der Chemie, TU Braunschweig, Germany (2008).

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S. K. Adla, G. Golz, T. Lindel, "NBS-induced *tert*-Prenyl Rearrangements on Tryptamines" (Poster). 2$^{nd}$ German-Indian Symposium on "Frontiers of Chemistry", Leipzig, Germany (2009).

S. K. Adla, N. Marsch, T. Lindel, "Synthesis and Oxidation of Prenylated Indole Alkaloids" (Poster). 17$^{th}$ Lecture Conference, ORCHEM 2010, Weimar, Germany (2010). Awarded with poster prize.

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S. K. Adla, T. Lindel, "Prenyl Rearrangements on Tryptamine Derivatives" (Poster). Wissenschaftsforum Chemie 2011, Bremen, Germany (2011).

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TO MY FAMILY

AND IN MEMORY OF MY FATHER

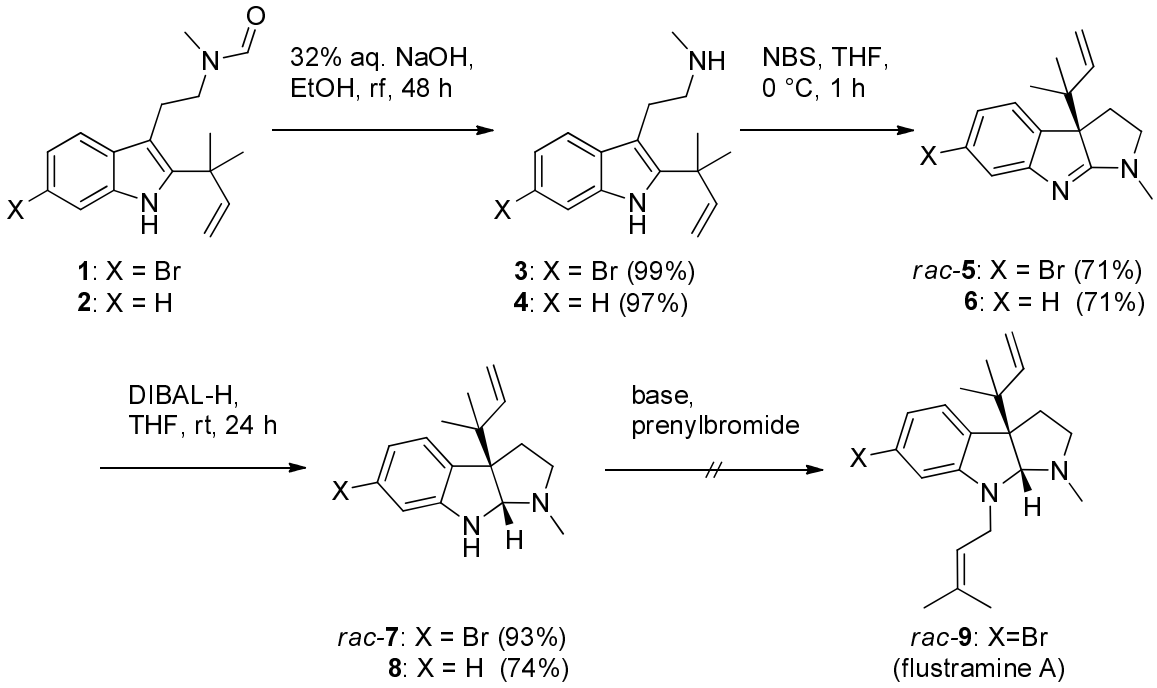
**Table of Contents**

# 1 Summary

*Flustra foliacea* is a marine bryozoan found in the waters of Nova Scotia, the North Sea and the White Sea (Russia) and has been a rich source of mono- and diterpenoids and 32 indole alkaloids. Most of the *Flustra* alkaloids are brominated and possess prenyl (3,3-dimethylallyl) and/or *tert*-prenyl (1,1-dimethylallyl) groups located at various positions. The chemical synthesis of *Flustra* alkaloids and subsequent biological evaluation of the synthetic natural products and analogues was the subject of this thesis work.

*a. Synthesis of flustramine C, dihydroflustramine C and debromo analogues*

Flustrabromine (**1**) was synthesized from tryptamine (**124**) with an overall yield of 29% in 5 steps. The natural product **1** was deformylated to deformylflustrabromine (**3**) in excellent yield. In the key step, **3** was subjected to Lindel's oxidative 2-*tert*-prenyl rearrangement conditions. On reaction with NBS at 0 °C cyclization and sigmatropic [1,5] shift of the 2-*tert*-prenyl group was induced to result in *rac*-flustramine C (**5**) in a one pot transformation. No brominated side products were detected. Formation of **5** is most straight forward and possibly biomimetic.




Scheme 1: NBS-induced oxidative rearrangement of 2-*tert*-prenyltryptamines.

*Rac*-flustramine C (**5**) was diastereoselectively reduced by DIBAL-H to result in *rac*-dihydroflustramine C (**7**, 93%). However, prenylation of **7** did not lead to the formation of *rac*-flustramine A (**9**). Instead, degradation occurred.

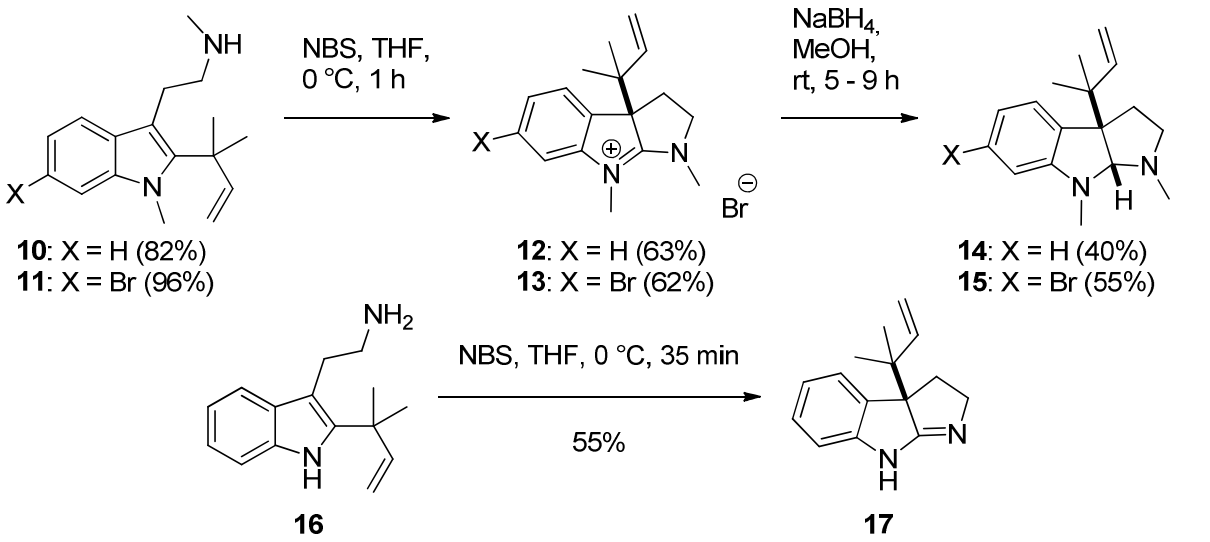
Application of Lindel's rearrangement conditions on **3** worked well. Secondary amine **3** upon reaction with NBS underwent cyclization/rearrangement to furnish *rac*-debromoflustramine C (**6**). Similarly, reduction of **6** furnished *rac*-debromodihydroflustramine C (**8**) for the first time (Scheme 1).

Reaction of deformylflustrabromine (**3**) with NBS, NCS, and NIS furnished *rac*-flustramine C (**5**) in every case with reaction times of 20-60 minutes, 2 d, and 3-7 hours, respectively. The individual enantiomers of *rac*-flustramine C (**5**) were separated on a chiral HPLC column. The optical rotation for the enantiomer of **5** with the lower retention time (6.2 min) was $[\alpha]_D^{21.6}$ = +153 ° (*c* = 7.9 mg/mL, $CHCl_3$) while the enantiomer of **5** with the higher retention time (8.1 min) showed an optical rotation of $[\alpha]_D^{21.8}$ = –155 ° (*c* = 8.1 mg/mL, $CHCl_3$). The hypervalent iodine reagent PIFA (Phenyliodo(III)bis(trifluoroacetate)) formed **5** in low yield (5%).

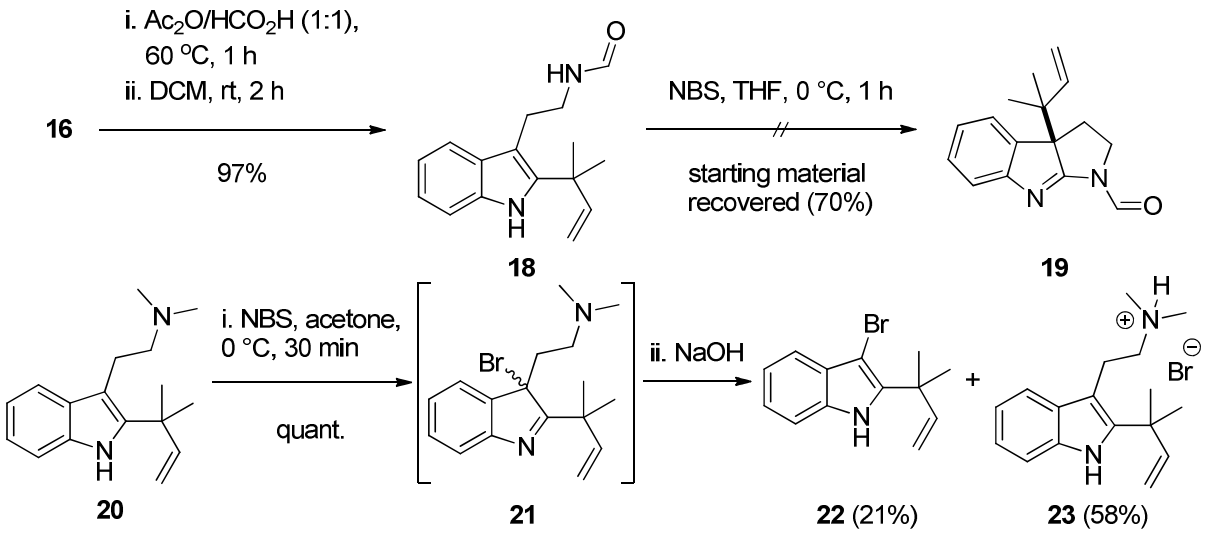
*b. Scope of the NBS-induced rearrangement on 2*-tert-*prenyltryptamines*

The scope of Lindel's oxidative 2-*tert*-prenyl rearrangement reaction was evaluated on structurally varied derivatives. NBS-induced cyclization and prenyl shift on **10** to furnish the dimethylated amidinium salt **12**. The debromo analog **11** behaved in the same way to result in formation of **13**. The salts **12** and **13** were diastereoselectively reduced by $NaBH_4$ to form the $N_a$-methyl-dihydroflustramine C (**14**) and debromo analogue **15**, respectively. In the next case study, the methyl group at the aliphatic amino group was omitted. Reaction of **16** *via* NBS-induced oxidative cyclization and rearrangement of the 2-*tert*-prenyl group resulted in pyrrolo[2,3-*b*]indole **17** in moderate yield (Scheme 2).

However, $N_b$-formylated precursor **18** failed to undergo oxidation on reaction with NBS. The behavior of $N_b$,$N_b$-dimethyl indole **20** was surprising. Compound **20** was treated with NBS to generate transient bromoindolenine **21** which was characterized by NMR spectroscopy. After work-up with 2 M NaOH, 3-bromo-2-*tert*-prenylindole (**22**) and HBr salt of the starting material (**23**) were the only isolated products (Scheme 3).




Scheme 2: Presence/absence of alkyl substitution did not influence the cyclization/prenyl shift sequence.

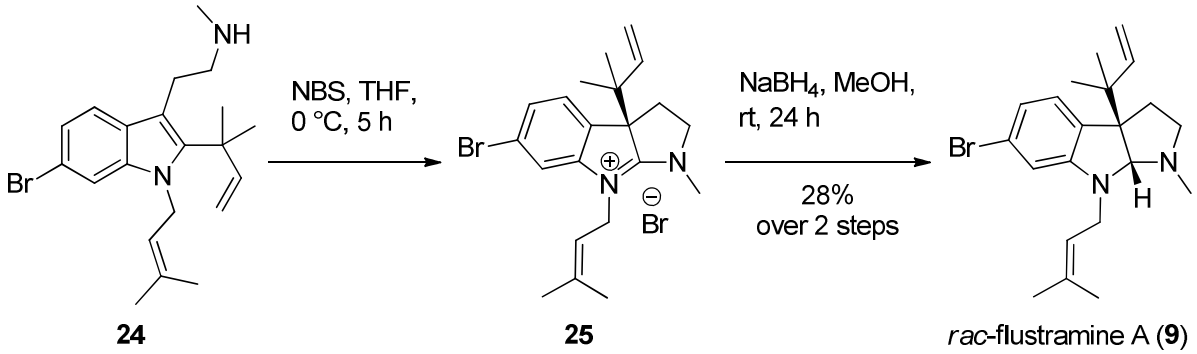



Scheme 3: NBS failed to rearrange the 2-*tert*-prenyl group when the aliphatic side chain contained either a formamide or a tertiary amine.

The above results indicated that the bromine substituent is not required for the oxidative transformation. The methyl group at indole N-1 or an aliphatic amine do not disturb the cyclization/prenyl shift sequence whereas presence of the proton at the side-chain amine is necessary. However, if the side chain beared an amide or a tertiary amine moiety, no formation of pyrrolo[2,3-*b*]indoles was observed.

*c. Synthesis of* rac-*flustramine A*

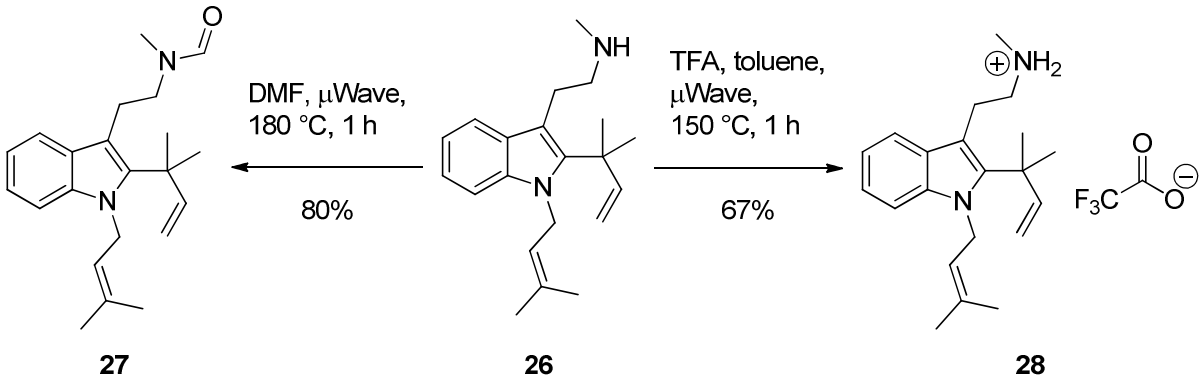
The doubly prenylated indole **175** was deformylated to **24**. Secondary amine **24** was reacted with NBS in THF to undergo oxidative ring closure/sigmatropic [1,5] shift of 2-*tert*-prenyl group to form the amidinium salt **25**. The salt **25** was subsequently reduced by $NaBH_4$ to furnish *rac*-flustramine A (**9**) in a combined yield of 28% over the last two steps (Scheme 4).




Scheme 4: Synthesis of *rac*-flustramine A (**9**) from **24**.

*d. Study on doubly prenylated indole under non oxidative conditions*

Doubly prenylated **26** was thermally stable and attempts to rearrange the prenyl group from indole N-1 under microwave conditions failed. In one experiment, DMF was used to add a formyl group to **27** whereas TFA salt **28** was formed in another experiment (Scheme 5).

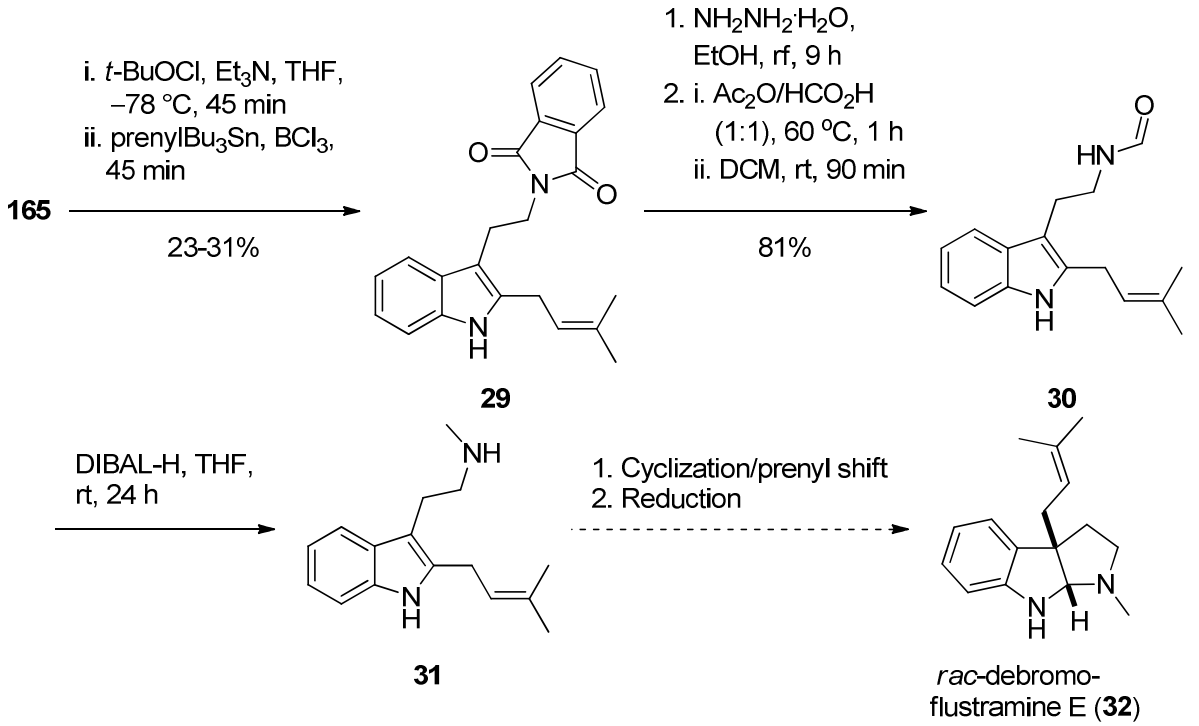



Scheme 5: Doubly prenylated indoles were thermally stable.

*e. Attempts towards the synthesis of debromoflustramine E*

It was envisaged that the regularly prenylated precursor **31** upon reaction with NBS would furnish debromoflustramine E (**32**). Danishefsky's protocol worked for the indole derivative **29** albeit in low yields. Hydrazinolysis of **29** followed by formylation

resulted in the formamide indole **30** in 81% over two steps. Although amide **30** was reduced with DIBAL-H to furnish **31**, efforts to obtain pure **31** were not fruitful as **31** degraded readily (Scheme 6).




Scheme 6: Synthesis of 2-prenyl-methyltryptamine (**31**).

*h. Biological evaluation of* Flustra *alkaloids and analogues*

Compounds deformylflustrabromine (**3**), flustramine C (**5**), and **Li-74**, **175**, and **24** were thoroughly screened against a panel of different 42 human cancer cell lines. $N_a$-prenyl-deformylflustrabromine (**24**) showed highest cytotoxicity with a geometric mean $IC_{50}$ value of 5.14 µM (Table 9). Compounds **175**, **3**, **Li-74**, and **5** showed geometric mean $IC_{50}$ values of 21.2, 30.5, 36.7, and 43.4 µM, respectively. When tested for antimicrobial activity, compounds **24** and **26** showed $IC_{50}$ values of 5.9, 7.7 µM, and 22.6, 7.7 µM against the gram positive bacteria *Micrococcus luteus* and *Mycobacterium phlei*, respectively. An $IC_{50}$ of 29 µM was observed for compound **26** against the gram negative bacterium *E.coli*. None of the compounds were antifungal. For bacterial biofilm inhibition, all the compounds were tested at concentrations of 1, 5, and 25 µM. Only compound **29** was active.

# 2 Introduction

## 2.1 Natural products

Natural product chemistry is important for medicine. From 1981 to 2010, 1130 new chemical compounds were approved as drugs with natural products (47) and natural product derivatives (247) being the major contributors. The majority of the newly approved medicinal agents were anticancer, antibacterial, antiviral, antihypertensive, and anti-inflammatory drugs in a number of 128, 118, 110, 79, and 51, respectively. Starting from 1940s to date, 48.6% of the small molecules used against Cancer were either natural products or derived from them.[1]

Marine organisms produce a wide variety of natural products in response to the challenging environmental conditions. These natural products often exhibit high structural diversity and complexity. With interesting biological activities, they represent the leading scaffolds in drug discovery and development. Pharmaceutical research involving marine natural products gained interest only in the last three decades. Didemnins[2] are a class of marine natural products with impressive *in vitro* and *in vivo* cytotoxicity (in concentrations below nM) resulting in the first human clinical trials in U.S. (up to Phase II).[3] Another example is bryostatin 1 from the bryozoan *Bugula neritina*.[4] Bryostatin 1 has been in at least 80 human clinical trials from which 20 trials completed phase I and phase II.[5] Dolastatin 10 and its analogue symplostatin 1 isolated from the marine cyanobacterium *Symploca* sp. VP642 are microtubule inhibitors with effective depolymerisation ability on murine mammary tumors.[6] The synthetic derivative soblidotin is in clinical trials phase II and more active than the natural product Dolastatin 10.[7] Sponge derived compounds discodermolide (from *Discodermia dissoluta*), ecteinascidin 743 (from *Ecteinascidia*

1. D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311–335.
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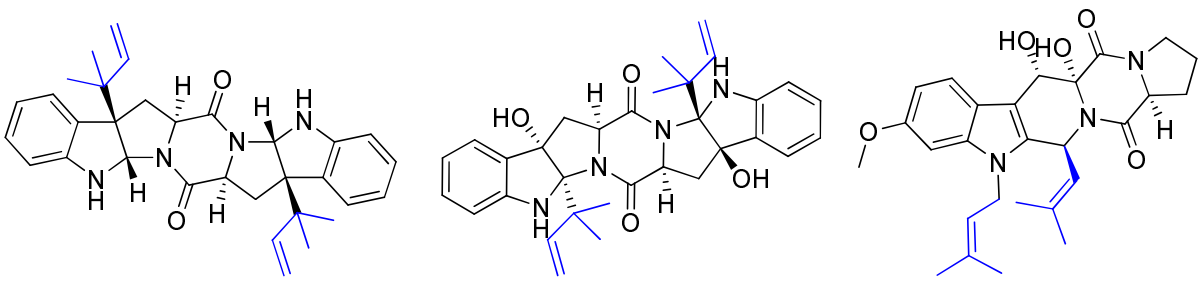
*turbinata*), applidine (from *Tridemnum solidum*) and kahalalide F (from *Elysia rufescens*) are in clinical trials.[8]

Most of the marine natural products are alkaloids and halogenated compounds.[9] Presence of bromine and chlorine is a most common scenario..[10] Moreover, heterocyclic core structures such as indole are a common motif in many natural products. A few examples of bis-indole alkaloids[11] include dendridine A, anti-corrosive caulerpin, and hyrtiazepine whereas tris-indoles such as gelliusines[12] also exist.

Non-marine indole alkaloids functinalized with either prenyl and/or *tert*-prenyl groups are represented by amauromine (**33**),[13] gypsetin (**34**),[14] fumitremorgin B (**35**)[15], and brevianamide, to name a few (Figure 1).



amauromine (**33**) gypsetin (**34**) fumitremorgin B (**35**)

Figure 1: Structures of pyrrolo[2,3-*b*]indole natural products functionalized with prenyl and/or *tert*-prenyl groups.

Marine natural products sharing similar structural features to **33**, **34**, and **35** are flustramines (see Section 2.2.1) which have been isolated from the marine bryozoan *Flustra foliacea* (see Section 2.2).

8. G. M. Cragg, D. J. Newmann, *Pure Appl. Chem.* **2005**, *77*, 1923–1942.
9. P. M. Pauletti, L. S. Cintra, C. G. Braguine, A. A. d-S. Filho, M. L. A. Silva, W. R. Cunha, A. H. Januário, *Mar. Drugs* **2010**, 8, 1526–1549.
10. C. S. Neumann, D. G. Fujimori, C. T. Walsh, *Chem. Biol.* **2008**, *15*, 99–109.
11. (a) M. Tsuda, Y. Takahashi, J. Fromont, Y. Mikami, J. Kobayashi, *J. Nat. Prod.* **2005**, *68*, 1277–1278. (b) C. Kamal, M. G. Sethuraman, *Ind. Eng. Chem. Res.* **2012**, *51*, 10399–10407. (c) P. Sauleau, M.-T. Martin, M.-E. T. H. Dau, D. T. A. Youssef, M.-L. Bourguet-Kondracki, *J. Nat. Prod.* **2006**, *69*, 1676–1679.
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### *2.2 Flustra foliacea*

*Flustra foliacea* is a cheilostome marine bryozoan (Figure 2) commonly found at a depth of 15-20 meters. The larvae of *F. foliacea* selectively settle at the initially explored site. The mucopolysaccharide secretion facilitates a temporary attachment onto the surface followed by the protein secretions from the internal sac of the bryozoan to make this attachment rigid and permanent.[16]

Figure 2: *Flustra foliacea*.[17]

*F. foliacea* has an annual growth season between March and November with exponential addition of zooids. The frontal buds have the capacity of giving rise to new branches of fronds. Thickening of the frontal fronds leads to strengthening of the holdfast.[18] The slow growing *F. foliacea* can be cultivated in the laboratory under defined conditions.[19] Recently, the mitochondrial genome of *F. foliacea* was sequenced.[20]

*Flustra foliacea* is an abundant source for terpenes and heterocyclic natural products having an indole core decorated with prenyl and/or *tert*-prenyl groups at various positions. .

16. M. J. Loeb, G. Walker, *Mar. Biol.* **1977**, *42*, 37–46.
17. (a) Figure on Left: online at http://www.habitas.org.uk/marinelife/species.asp?item=Y6940, on 11/11/2012. (b) Figure on right: with permission from Jason Gregory on 10/09/2009.
18. A. R. D. Stebbing, *Mar. Ecol.* **1971**, *9*, 267–273.
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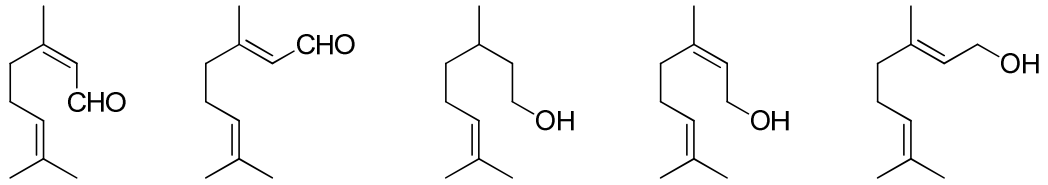
### 2.2.1 Isolation

GC-MS analysis of the volatile constituents from *Flustra foliacea* by Christophersen and Carlé resulted in the identification of five known compounds, *cis*-citral (**36**), *trans*-citral (**37**), citronellol (**38**), nerol (**39**), and geraniol (**40**, Figure 3).[21]




**36** **37** **38** **39** **40**

Figure 3: Volatile constituents isolated from *Flustra foliacea*

Christophersen et al. continued the search and were able to isolate the first *Flustra* alkaloids, possessing a physostigmine skeleton, namely flustramine A (**9**) and flustramine B (**41**).[22] Structural assignment was unambiguously done utilizing standard methods of mass spectrometry, MCD (Magnetic Circular Dichroism), UV, IR, and NMR spectroscopy. Flustramine A (**9**) bears an inverted prenyl (1,1-dimethylallyl) group at C-3 of the indoline nucleus whereas flustramine B (**41**) exhibits a 3,3-dimethylallyl unit at C-3. Nuclear Overhauser enhanced $^{1}$H NMR experiments revealed that bromine was present at the 6-position and that the pyrrolidino ring was *cis* fused.[23]

In 1981, Carlé and Christophersen isolated the oxidized versions of **9** and **41**, namely flustraminol A (**42**) and flustraminol B (**43**) along with the identification of flustramine C (**5**). Extensive spectroscopic studies indicated the presence of bromine at C-6 and a fused pyrrolo[2,3-*b*]indole system in all of the new natural products. The position of the inverse prenyl group was at C-3a in flustramine C (**5**) and at C-8a in the case of flustraminol A (**42**). Flustraminol B (**43**) contained the regular prenyl (3,3-dimethylallyl) group at N-8 of the cyclic system.[24] They also reported the isolation and structure elucidation of flustrabromine (**1**), which occurs in the form of two

21. C. Christophersen, J. S. Carlé, *Naturwissenschaften* **1978**, *65*, 440–441.
22. S. Carlé, C. Christophersen, *J. Am. Chem. Soc.* **1979**, *101*, 4012–4013.
23. J. S. Carlé, C. Christophersen, *J. Org. Chem.* **1980**, *45*, 1586–1589.
24. J. S. Carlé, C. Christophersen, *J. Org. Chem.* **1981**, *46*, 3440–3443.

rotational isomers in the NMR ($CDCl_3$, room temperature), of flustramide A (**44**) and of 6-bromo-$N_b$-formyl-$N_b$-methyltryptamine (**45**, Figure 4).[25,26]

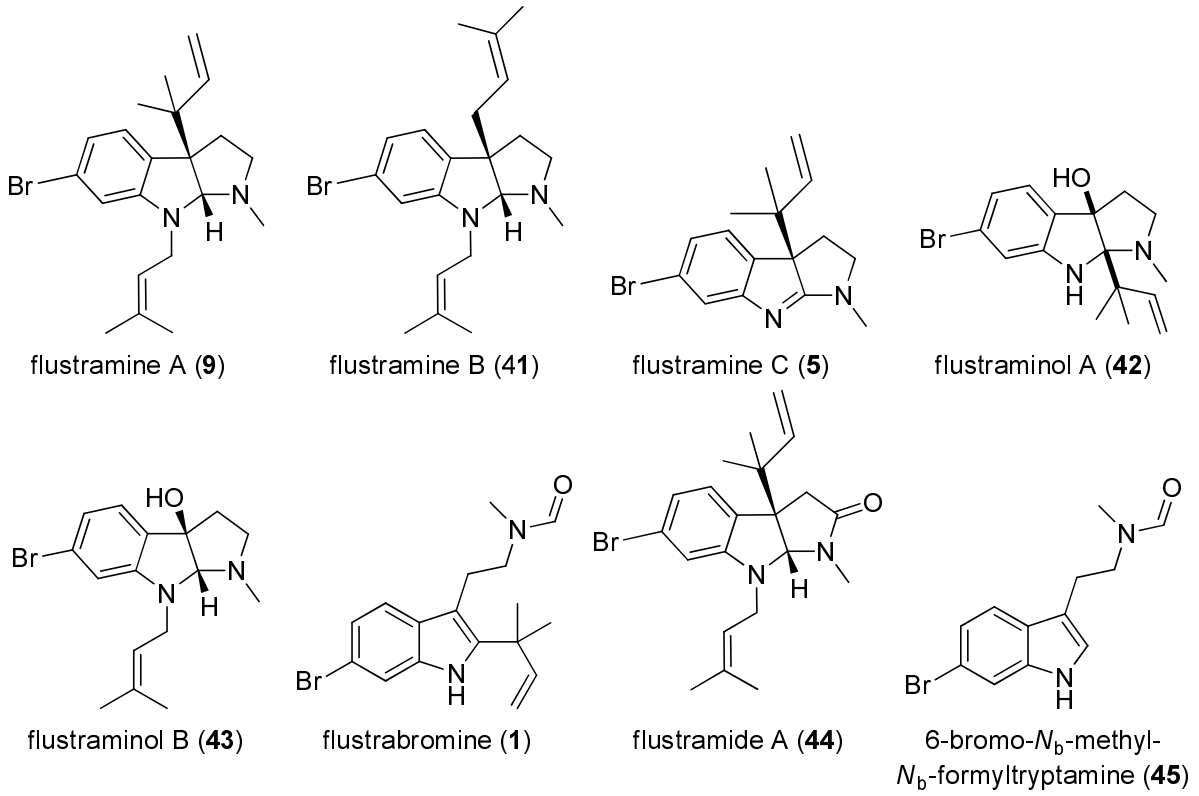



Figure 4: Indole alkaloids isolated from *F. foliacea* by Christophersen et al.[25,26]

Wright tested the crude dichloromethane extract from *F. foliacea* against *B. subtilis* and, utilizing assay guided fractionation, isolated the alkaloid dihydroflustramine C (**7**)[27] as one of the major metabolites, along with dihydroflustramine C *N*-oxide (**46**), flustramine D (**47**), flustramine D *N*-oxide (**48**), and isoflustramine D (**49**, Figure 5).[28] The subsequent members to be isolated were flustramine E (**50**), and debromoflustramine B (**51**) from the Danish west coast waters of the North Sea.[29] Gas-phase extraction with diethyl ether led to the identification of a citral dimer **52**, probably being a work-up artifact.[30]

25. P. Wulff, J. S. Carlé, C. Christophersen, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2895–2898.
26. P. Wulff, J. S. Carlé, C. Christophersen, *Comp. Biochem. Physiol.–B: Biochem. Mol. Biol.* **1982**, *71* (3), 523–524.
27. J. L. C. Wright, *J. Nat. Prod.* **1984**, *47*, 893–895.
28. M. V. Laycock, J. L. C. Wright, J. A. Findlay, A. D. Patil, *Can. J. Chem.* **1986**, *64*, 1312–1316.
29. P. B. Holst, U. Anthoni, C. Christophersen, P. H. Nielsen, *J. Nat. Prod.* **1994**, *57*, 997–1000.
30. P. B. Holst, U. Anthoni, C. Christophersen, P. H. Nielsen, K. Bock, *Acta Chem. Scand.* **1994**, *48*, 765–768.

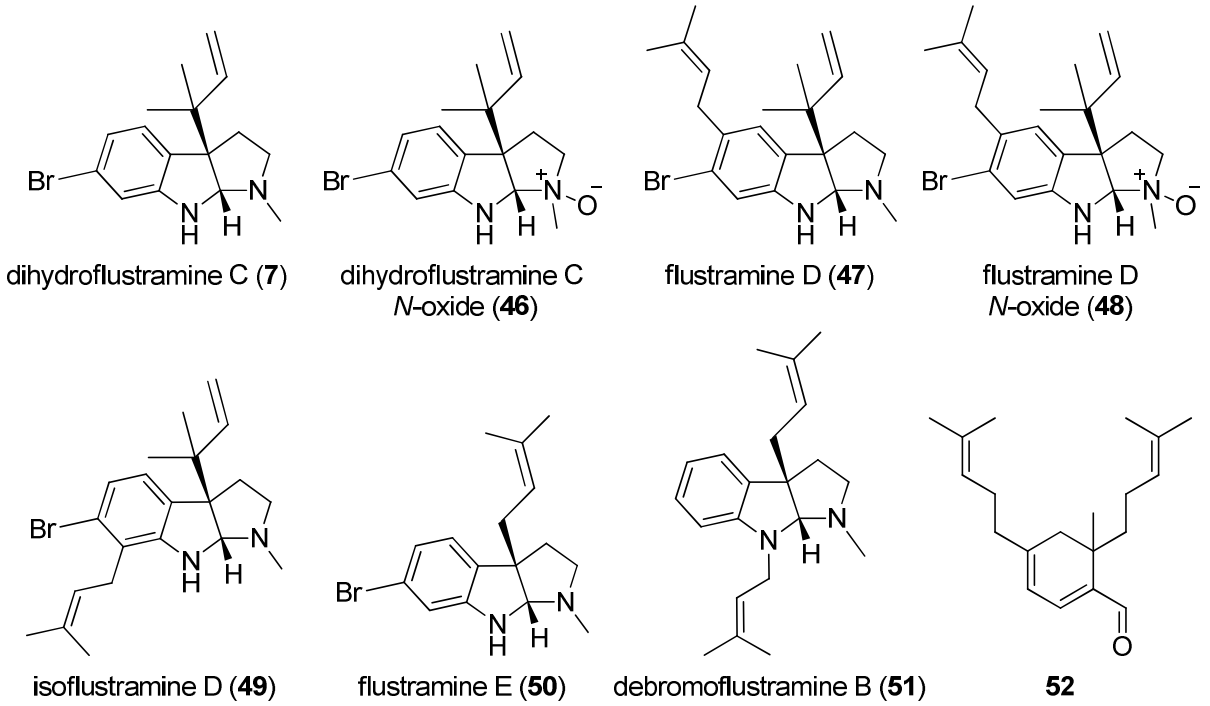



Figure 5: Natural products isolated from the bryozoan *F. foliacea.*

Interestingly, under similar conditions, Peters, König, et al. re-isolated the citral dimer **52**, flustramine A (**9**), flustramine C (**5**), flustraminol A (**42**), flustrabromine (**1**), dihydroflustramine C (**7**), and flustramine D (**47**), along with five new bromo-indole alkaloids **53** – **56**.[31,32] Alkaloid **53** shows a physostigmine core decorated with a geranyl group at the bridgehead 3a-position, while the remaining three alkaloids **54**, **55**, and deformylflustrabromine (**3**) contained an indole core substituted with a *tert*-prenyl group at indole C-2 (Figure 6). Lysek, Lindel, et al. re-isolated the natural products flustramine A (**9**), dihydroflustramine C (**7**), flustramine D (**47**), and deformylflustrabromine (**3**).[33] Peters, König, et al. reported the isolation of deformylflustrabromine B (**56**)[34] and a study on the variation in concentrations of indole alkaloids from *F. foliacea* (Figure 5 andFigure 6).[35]

31. L. Peters, G. M. König, H. Terlau, A. D. Wright, *J. Nat. Prod.* **2002**, *65*, 1633–1637.
32. L. Peters, G. M. König, A. D. Wright, R. Pukall, E. Stackebrandt, L. Eberl, K. Riedel, *Appl. Environ. Microbiol.* **2003**, *69*, 3469–3475.
33. N. Lysek, E. Rachor, T. Lindel, *Z. Naturforsch.* **2002**, *57c*, 1056–1061.
34. L. Peters, A. D. Wright, S. Kehraus, D. Gündisch, M. C. Tilotta, G. M. König, *Planta Med.* **2004**, *70*, 883–886.
35. L. Peters, A. D. Wright, A. Krick, G. M. König, *J. Chem. Ecol.* **2004**, *30*, 1165–1181.

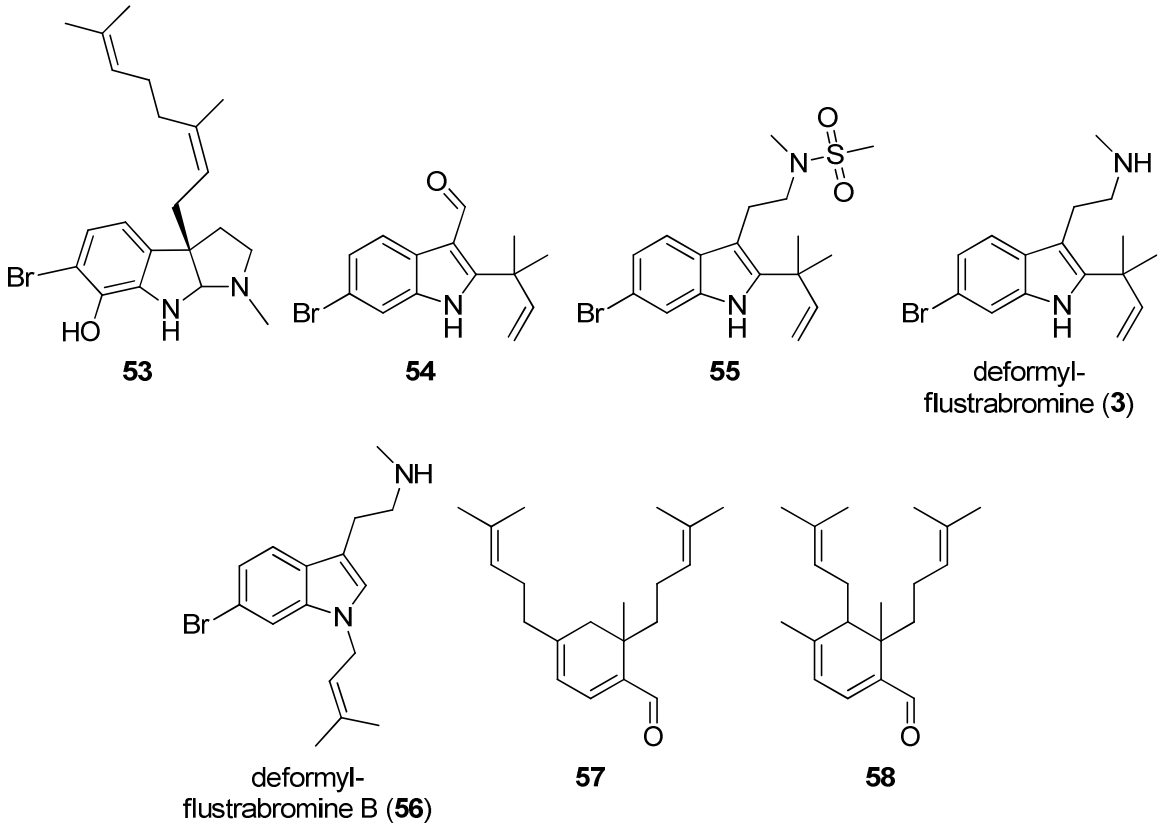



Figure 6: Natural products isolated from the bryozoan *Flustra foliacea.*

Recently, Rochfort, Wright, et al. reported the isolation of new flustramines from Canadian waters[36] possessing complex structures with varied functionalities and designated as flustramines F–P (**59** – **70**, Figure 7). Flustramine F (**59**) is an $N_1$-acetylated version while flustramine G (**60** is a dibrominated analogue of dihydroflustramine C (**7**). Flustramine H (**61**) and debromoflustramine H (**62**) possessed a geranyl and a hydroxyl group whereas flustramine I (**63**) is prenylated. Flustramine J (**64**) and K (**65**) were the dibromo analogues of flustramines H (**62**) and I (**63**). Flustramine L (**66**) was a hydroxylated isomer of flustramine D (**47**) whereas flustramine M (**67**) contained an oxidized prenyl group at the benzene section of the molecule. Interestingly, flustramine N (**68**) exhibits a benzofuro[2,3-*b*]pyrrole core structure functionalized with an amino-, a bromo-, and a prenyl group at the 4-, 5-, and 7- positions, respectively. Flustramine O (**69**) is a pseudodimer with two units of dihydroflustramine C (**7**) connected by a methylene bridge, whereas flustramine P (**70**) was also a pseudodimer comprising dihydroflustramine C (**7**) and

36. S. J. Rochfort, S. Moore, C. Craft, N. H. Martin, R. M. van Wagoner, J. L. C. Wright, *J. Nat. Prod.* **2009**, *72*, 1773–1781.

flustramine H (**61**) joined by a methylene bridge. The authors propose that **69** and **70** might be isolation artifacts.

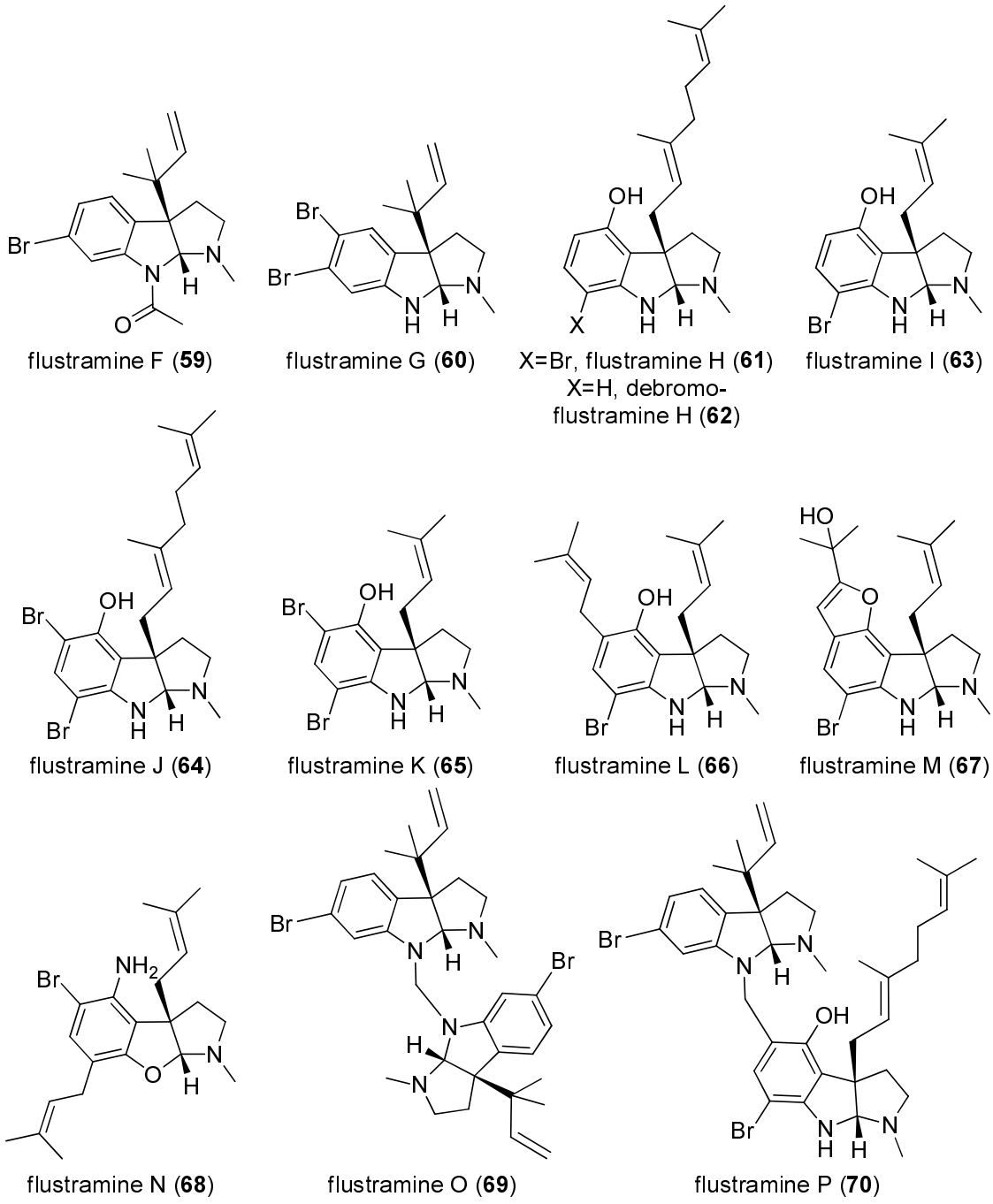



Figure 7: *Flustramines* isolated by Rochfort, Wright, et al.

### 2.2.2 Synthesis of flustramines – a literature survey

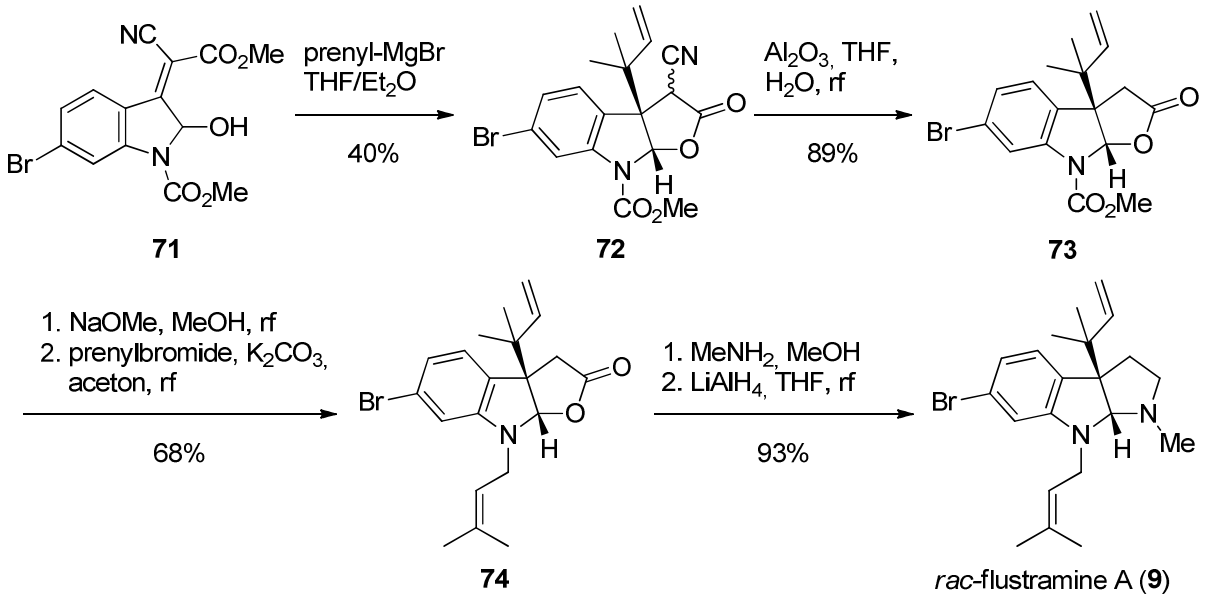
#### 2.2.2.1 Total syntheses of flustramine A

Morales-Ríos, Joseph-Nathan, et al. developed a facile method via addition of organomagnesium species to 2-hydroxy indolenines introducing an alkyl moiety at the 3-position of indole. This methodology was extended to advanced intermediates which, in turn, enabled the first total syntheses of flustramine A (**9**) and B (**41**), flustramide A (**44**) and B and debromoflustramine B (**51**).[37]

The synthesis of flustramine A (**9**) started at an advanced intermediate **71** which was prepared from an appropriately substituted 3-acetonitrilindole.[38] 2-Hydroxyindolenine **71** was stirred with 4 equivalents of prenylmagnesiumbromide in anhydrous THF/ether at –78 °C resulting in the formation of C-3 *tert*-prenylated endo isomer **72** and the C-3 prenylated analogue (not shown in Scheme 7) in a combined yield of 76% with a ratio of 53:47. The reason for the formation of two products was attributed to the formation of equilibrium between prenylmagnesiumbromide with its more stable 1,1-dimethylallyl isomer.

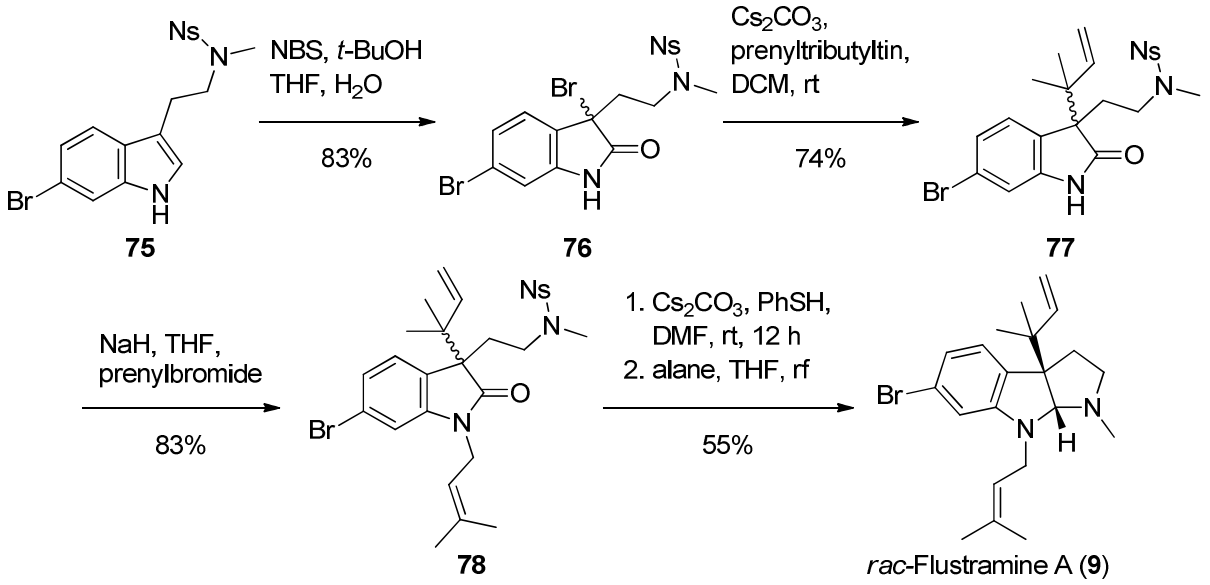
In the presence of wet alumina, α-cyano-γ-lactone **72** was subjected to hydrolytic decyanation in refluxing THF. The electron-withdrawing *N*-$CO_2$Me substituent of **73** was cleaved-off by refluxing in methanolic NaOMe and immediate treatment with $K_2CO_3$/prenylbromide in boiling acetone to give the lactone **74** (68% over two steps). Lactamization of the lactone **74** to flustramide A (**44**) was achieved by treating it with methylamine in MeOH at room temperature in 98% yield. Finally, the reduction of **44** using $LiAlH_4$ at room temperature furnished the natural product flustramine A (**9**, 96%) with an overall yield of 23% over six steps (Scheme 7).

37. M. S. Morales-Ríos, O. R. Suárez-Castillo, J. J. Trujillo-Serrato, P. Joseph-Nathan, *J. Org. Chem.* **2001**, *66*, 1186–1192.
38. M. S. Morales-Ríos, M. A. Bucio, P. Joseph-Nathan, *J. Heterocycl. Chem.* **1993**, *30*, 953–956.




Scheme 7: First synthesis of (±)-flustramine A (**9**) as reported by Morales-Ríos and Joseph-Nathan et al.[37]

The second total synthesis of *rac*-flustramine A (**9**) was reported by Fuchs and Funk in 2005 (Scheme 8).[39] Working on base-promoted reactions of 3-alkyl-3-bromo-indoline-2-ones, they developed a facile method for introducing intra- and intermolecular nucleophiles/dienophiles into 3-bromo-indolin-2-ones.




Scheme 8: Concise synthesis of (±)-flustramine A as shown by Fuchs and Funk.[39]

39. J. R. Fuchs, R. L. Funk, *Org. Lett.* **2005**, *7*, 677–680.

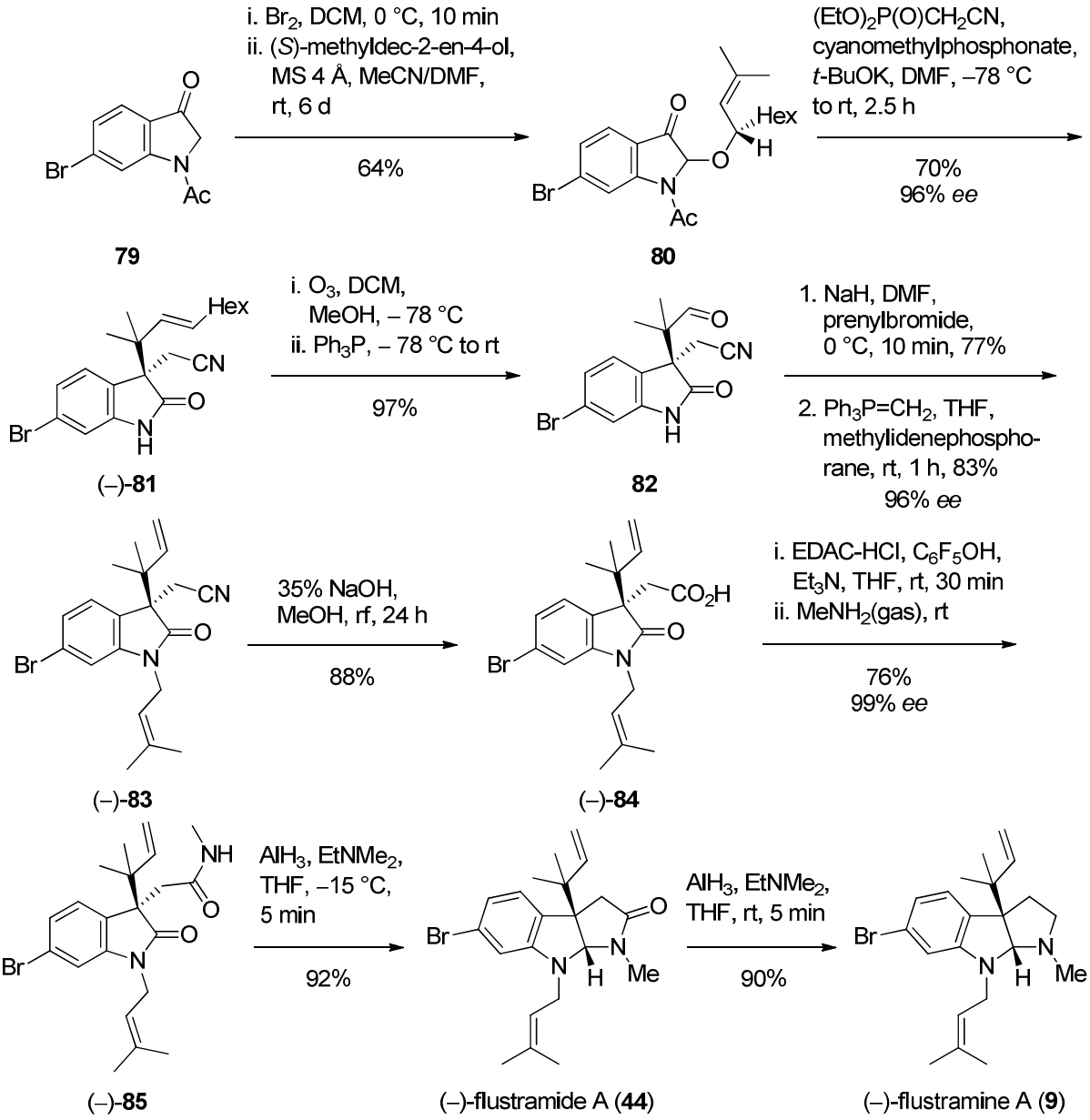
6-Bromoindole **75** afforded 3-alkyl-3-bromo-indolin-2-one **76** on reaction with NBS (*N*-bromosuccinimide). Reaction of compound **76** with caesium carbonate and prenyltributylstannane resulted in the introduction of the *tert*-prenyl unit at the indole C-3 (**77**, 74%). A second prenyl group was introduced by the standard procedure of treating the indol-2-one **77** with NaH/prenylbromide to give the doubly prenylated intermediate **78** in 83% yield. Deprotection of **78** using caesium carbonate, according to Fukuyama protocol,[40] and subsequent reduction by treatment with 1.1 equivalents of alane in THF led to the formation of *rac*-flustramine A (**9**, 55%) with a yield of 21% over 6 steps.

In 2006, Kawasaki et al. published the first enantioselective total synthesis of (–)-flustramine A (**9**), (–)-flustramine B (**41**), (–)-flustramide A (**44**), and (–)-flustramide B *via* a domino olefination–isomerization–Claisen rearrangement and reductive cyclization (Scheme 9).[41]

The synthesis started with the preparation of optically active (*S*)-methyldec-2-en-4-ol (99% *ee*) in moderate yield. Bromination of **79** and substitution with the synthetic (*S*)-methyldec-2-en-4-ol gave indolin-3-one **80** in 64% yield. In the next step, the intermediate **80** was allowed to react with cyanomethylphosphonate in a Horner–Wadsworth–Emmons olefination reaction. This resulted in consecutive isomerization, Claisen rearrangement of the prenyl group onto the indole C-3 followed by deacylation to provide the indolin-2-one intermediate (–)-**81** (70%, 96% *ee*). Ozonolysis of (–)-**81** resulted in an unstable aldehyde **82**, which underwent $N_a$-prenylation and Wittig olefination to give the doubly prenylated advanced precursor (–)-**83**. Alkaline hydrolysis of the nitrile (–)-**83** gave the free acid (–)-**84** which upon condensation with methylamine *via* the pentafluorophenyl ester using EDAC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) furnished *N*-methylamide (–)-**85** (99% *ee*, 67% after recrystallisation). In the next key step of reductive cyclization, treatment of (–)-**85** with alane complex ($AlH_3 \cdot EtNMe_2$) at –15 °C resulted in the smooth conversion to (–)-flustramide A ((–)-**44**, 92%) while further reduction with the alane complex at room temperature completed the first enantioselective synthesis of (–)-flustramine A ((–)-**9**, 90%) with an overall yield of 15% in 9 steps (Scheme 9).

40. T.Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
41. T. Kawasaki, M. Shinada, D. Kamimura, M. Ohzono, A. Ogawa, *Chem. Commun.* **2006**, 420–422.

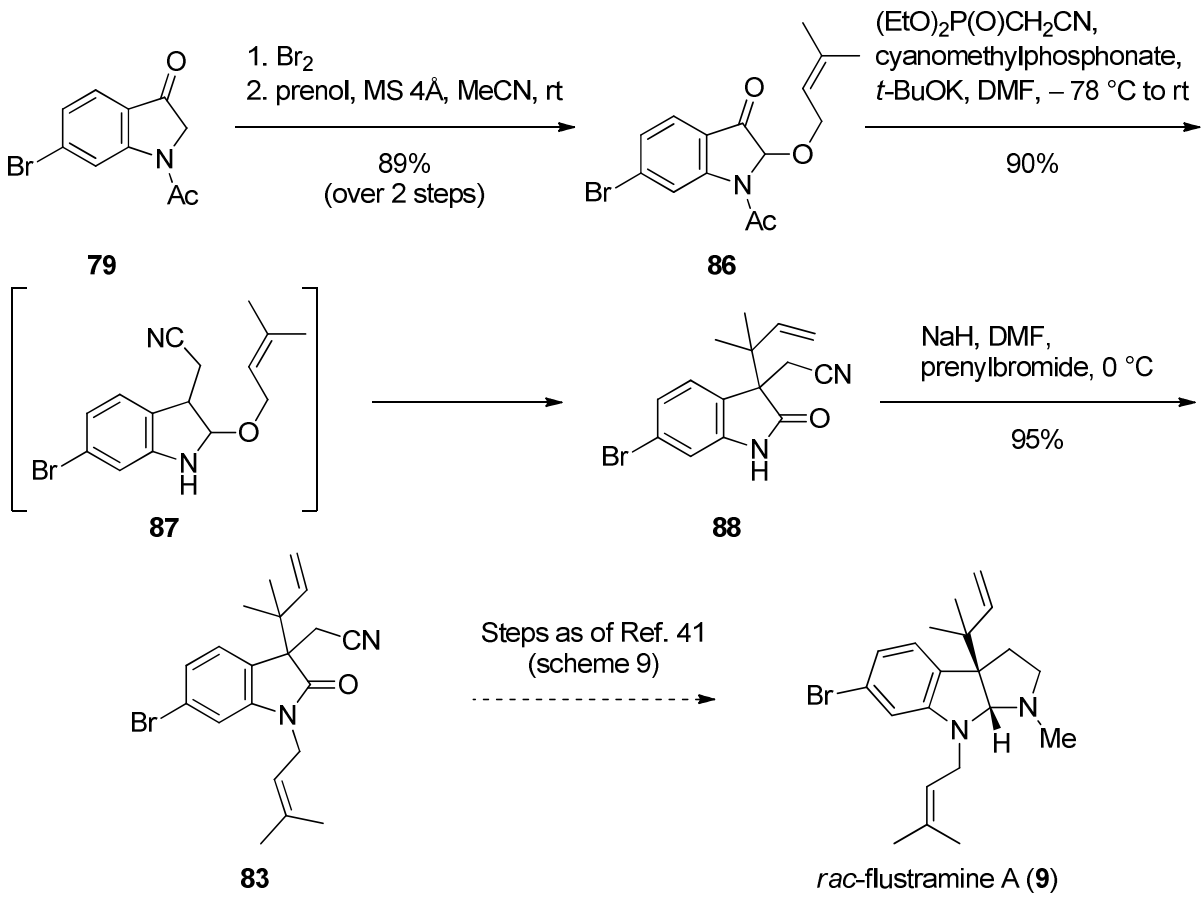
Kawasaki et al. also presented the total syntheses of (±)-flustramines A (**9**) and C (**5**), (±)-flustramide A (**44**) and (–)-debromoflustramine A, and (+)-debromoflustramine A.[42] By coupling with (*R*)-4-phenyloxazolidine-2-one, the (–)- and (+)- enantiomers of a carboxylic acid intermediate **84** were separated and carried forward to complete the syntheses of (–)- and (+)-debromoflustramines A (not shown in Scheme 9).




Scheme 9: Enantioselective synthesis of (–)-flustramine A (**9**) by Kawasaki et al.[41]

42. T. Kawasaki, M. Shinada, M. Ohzono, A. Ogawa, R. Terashima, M. Sakamoto, *J. Org. Chem.* **2008**, *73*, 5959–5964.

Bromination of 6-bromoindolin-3-one **79** at C-2, followed by substitution with prenol in the presence of molecular sieves (4Å) at room temperature provided the key molecule **86**. Compound **86** was exposed to cyanomethylphosphonate in the presence of *tert*-BuOK at –78 °C and allowed to warm to room temperature. This led to isomerization, Claisen rearrangement of the intermediate **86**, and deacetylation in a single pot to afford the C-3 *tert*-prenylated indolin-2-one **88** (90%). $N_a$-prenylation of **88** for the second time, followed by alkaline hydrolysis of the nitrile group and condensation with methylamine gave the amide **83**. Chemoselective reduction of this amide **83** using alane, as demonstrated previously (Scheme 9), resulted in the formation of (±)-flustramine A (**9**) *via* (±)-flustramide A (**44**). Thus far, this is the best synthesis of (±)-flustramine A (**9**) with a yield of 54% over 8 steps (Scheme 10).[42]

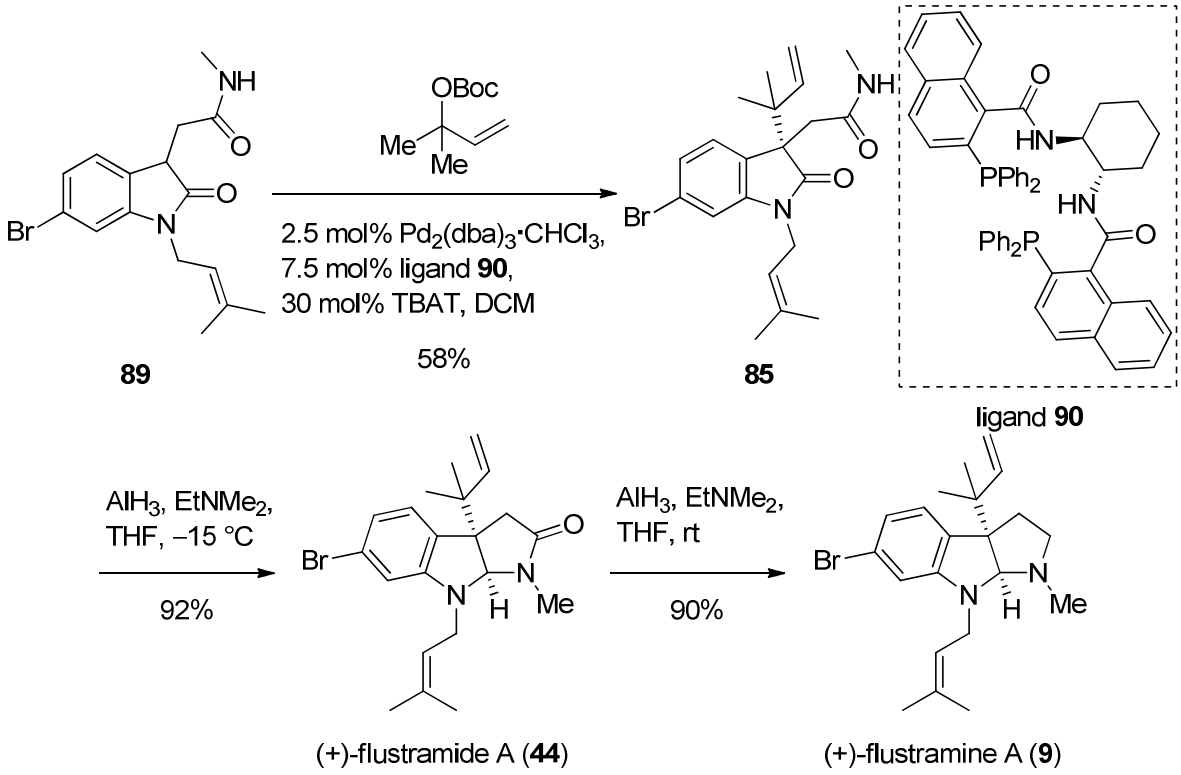



Scheme 10: Synthesis of (±)-flustramine A (**9**) by Kawasaki et al.[42]

One of the recent enantioselective syntheses of (+)-flustramine A (**9**) was shown by Trost et al. who developed a general palladium catalyzed asymmetric prenylation and geranylation process with high regio- and enantioselectivity.[43] After tuning the

43. B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.

selectivity toward *tert*-prenylation to optimal conditions with ligand **90** in DCM, $N_a$-prenylated precursor **89** was treated with 1.0 equivalent of the prenyl nucleophile, 2.5 mol% palladium(0) source, 7.5 mol% of the ligand **90**, and 30 mol% of the TBAT additive to furnish **85** with an excellent *ee* of 99%. Employing the conditions of Kawasaki et al., the doubly prenylated indole **85** was converted to (+)-flustramide A (**44**, 92%) and subsequently to (+)-flustramine A (**9**, 90%) with an overall yield of 16% in 5 steps (Scheme 11).

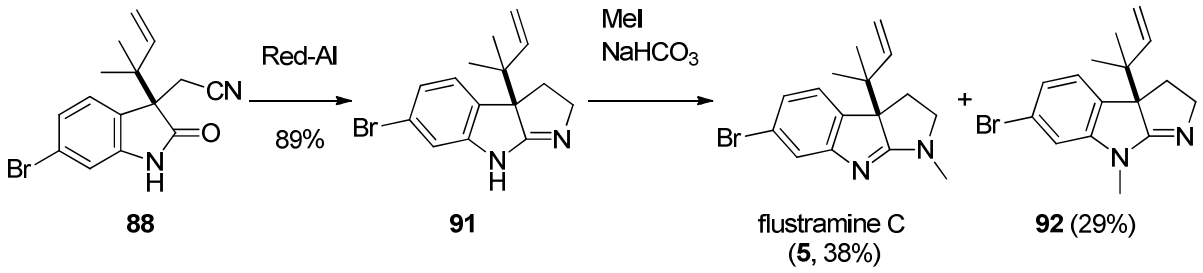



Scheme 11: Total synthesis of (+)-flustramine A by Trost et al.[43]

### 2.2.2.2 Total syntheses of flustramine C, dihydroflustramine C, and deformylflustrabromine

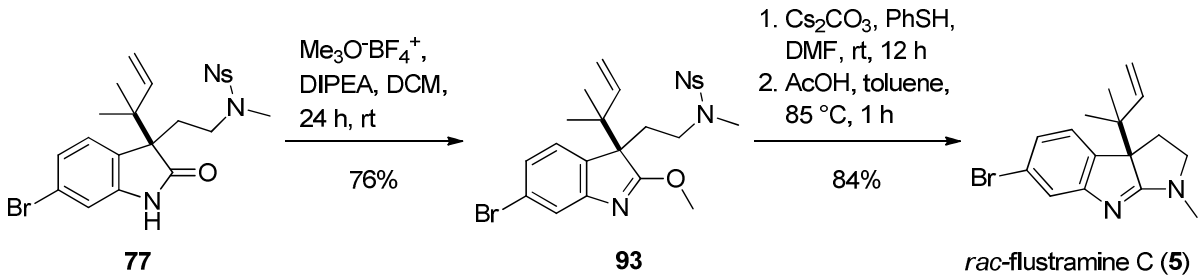
There are three total syntheses reported for flustramine C (**5**). Kawasaki et al. described the first synthesis of flustramine C (**5**). The synthesis commenced by exposure of the intermediate **88** to Red-Al to result in reductive cyclization to afford the tricyclic compound **91** (89%). Reaction of tricyclic compound **91** with methyliodide in the presence of sodium bicarbonate gave flustramine C (**5**, 38%) along with its regioisomer (**92**, 29%), completing the first total synthesis with an

overall yield of 9% in 8 steps (Scheme 12).[44] Without any further modification, Kawasaki et al. reported the synthesis again and described the use of the common intermediate **88** for the construction of (±)-flustramine A (**9**).[42]




Scheme 12: Total synthesis of (±)-flustramine C according to Kawasaki et al.[44]

Similarly, starting from the advanced precursor **77**, Fuchs and Funk showed the synthesis of *rac*-flustramine C (**5**). On reaction with the Meerwein salt **77** provided the imidate **93** (76%). Deprotection of the nosylamide functionality under Fukuyama conditions did not furnish *rac*-flustramine C (**5**). However, heating the crude deprotected amine mixture in toluene with one equivalent of acetic acid afforded *rac*-flustramine C (**5**, 84%) with an overall yield of 39% over five steps, starting from **75** (Scheme 13).[39]

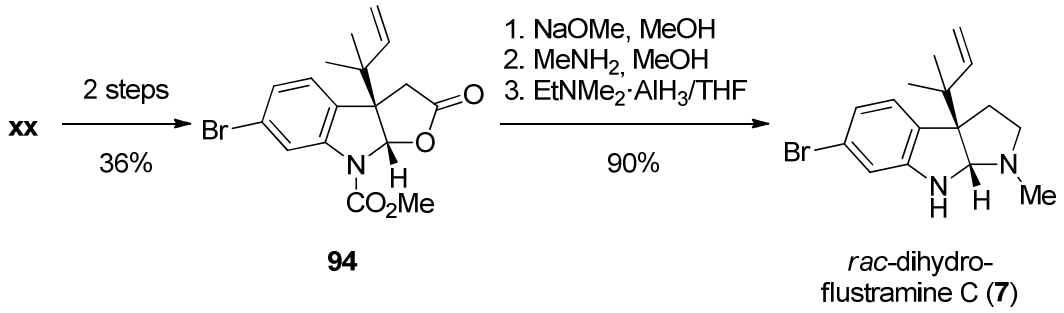



Scheme 13: Fuchs and Funk reported the total synthesis of (±)-flustramine C.[39]

There exists only one total synthesis for dihydroflustramine C (**7**). Using the synthetic route as in the case of flustramine A (**9**,Scheme 7),[37] Morales-Ríos, Joseph-Nathan, et al. synthesized dihydroflustramine C (**7**) and flustramine E (**50**) within five steps. The N-1 carboxylic ester was obtained within two steps from **71**. Saponification of **94** followed by reaction with methylamine, and reduction with alane complex furnished

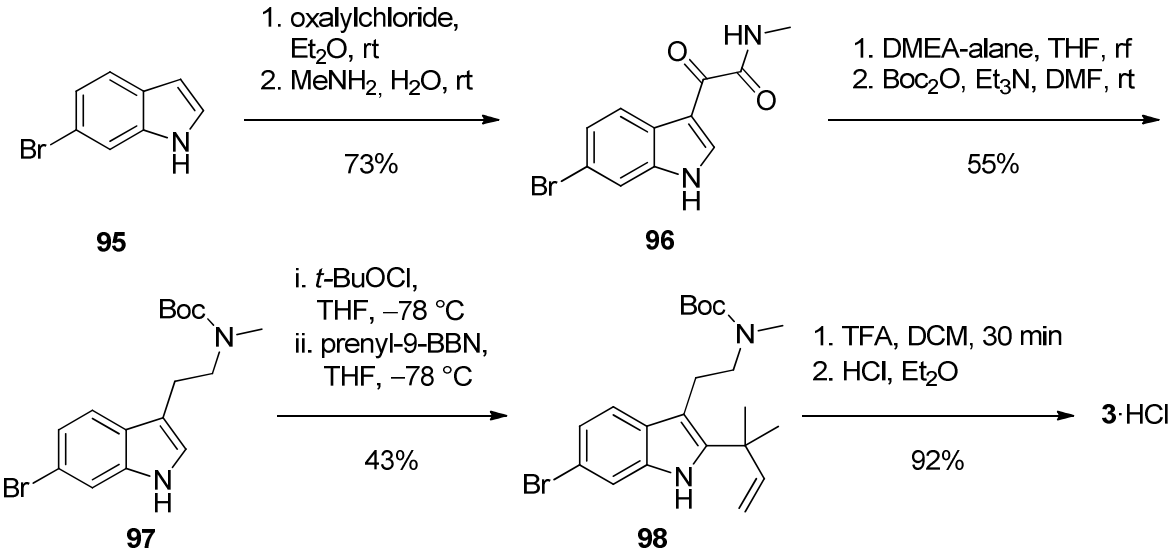
44. T. Kawasaki, R. Terashima, K.-e. Sakaguchi, H. Sekiguchi, M. Sakamoto, *Tetrahedron Lett.* **1996**, *37*, 7525–7528.

the natural product dihydroflustramine C (**7**) with an overall yield of 32% (Scheme 14).[45]




Scheme 14: Morales-Ríos, Joseph-Nathan, et al. reported the first synthesis of dihydroflustramine C (**7**).[37]

Kim and co-workers explored the synthesis of the HCl salt of **3** from 6-bromoindole (**95**) with 16% overall yield in 7 steps (Scheme 15).[46] Employing the Speeter/Anthony reaction on 6-bromoindole (**95**) and subsequent reduction and protection, the key compound **97** was obtained in 5 steps. Incorporation of 2-*tert*-prenyl group followed by deprotection and acidic treatment furnished the HCl salt of deformylflustrabromine.




Scheme 15: The HCl salt of deformylflustrabromine (**3**) was reported by Kim et al.[46]

45. M. S. Morales-Ríos, O. R. Suárez-Castillo, P. Joseph-Nathan, *Tetrahedron* **2002**, *58*, 1479–1484.

46. J.-S. Kim, A. Padnya, M. Weltzin, B. W. Edmonds, M. K. Schulte, R. A. Glennon. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4855–4860.

### 2.2.2.3 Syntheses of other *Flustra* alkaloids and analogues

Apart from the discussed syntheses of flustramine A (**9**), flustramine C (**5**), dihydroflustramine C (**7**), and deformylflustrabromine (**3**), there are several syntheses reported for the other members of the *Flustra* alkaloids. Table 1 highlights the syntheses of flustramine natural products while Table 2 summarizes the total syntheses of debrominated versions of the flustramines.

The work of Morales-Ríos made it possible to synthesize natural products flustramide A (**44**), flustramide B, flustramine A (**9**), flustramine B (**41**), and flustramine E (**50**) in good overall yields whereas Kawasaki et al. achieved the total syntheses of (–)-flustramide A (**44**), (–)-flustramide B, and (–)-flustramine B ((–)-**41**). However, the most elegant synthesis was published by Trost et al. who were able to achieve the synthesis of (+)-flustramide A ((+)-**44**) and (+)-flustramide B in two steps with overall yields above 50%. There are three total syntheses reported for each of the *rac*-flustramine B (**41**) and (–)-flustramine B (**41**) with the best overall yields being 24% and 58%, respectively. There are two equally good syntheses for the construction of flustramine E (**50**) while only one synthesis exists for each of the natural products (+)-flustramine B (**41**), *rac*-flustraminol B (**43**), (–)-flustraminol B (**43**), deformylflustrabromine (**3**), and deformylflustrabromine B (**56**). Table 1 provides an overview of the reported syntheses and compares each one of them in terms of number of steps and overall yield. As of today, there are no total syntheses published for the natural products flustramine D (**47**), as well as for the structurally challenging flustramines F–P (**59**–**70**).

Table 1: Reported syntheses of flustramines.

| Flustramine | Author | ∑ Steps | Overall Yield (%) |
|---|---|---|---|
| *rac*-flustramide A | M. S. Morales-Ríos (2001)[37] | 4 | 24 |
| (–)-flustramide A | T. Kawasaki (2006)[41] | 8 | 17 |
| (+)-flustramide A | B. M. Trost (2011)[43] | 2 | 53 |
| *rac*-flustramide B | M. S. Morales-Ríos (2001)[37]<br>D. Aburano (2007)[47] | 4<br>7 | 18<br>27 |
| (–)-flustramide B | T. Kawasaki (2006)[41] | 7 | 13 |

47. D. Aburano, T. Yoshida, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2007**, *72*, 6878–6884.

| Flustramine | Author | ∑ Steps | Overall Yield (%) |
|---|---|---|---|
| (+)-flustramide B | B. M. Trost (2011)[43] | 2 | 61 |
| *rac*-flustramine B | T. Hino (1983)[48] | 6 | 7 |
| | M. S. Morales-Ríos (2001)[37] | 5 | 17 |
| | D. Aburano (2007)[47] | 8 | 24 |
| (–)-flustramine B | J. F. Austin (2004)[49] | 7 | 58 |
| | T. Kawasaki (2006)[41] | 8 | 12 |
| | S. Kobayashi (2009)[50] | | |
| (+)-flustramine B | B. M. Trost (2011)[43] | 3 | 55 |
| *rac*-flustraminol B | O. R. Suárez-Castillo (2007)[51] | | |
| (–)-flustraminol B | N. Hara (2011)[52] | | |
| flustramine E | M. S. Morales-Ríos (2002)[53] | 5 | 27 |
| | D. Aburano (2007)[47] | 7 | 28 |
| deformylflustrabromine B | J.-S. Kim (2007)[46] | 6 | 35 |

The synthesis of debrominated *Flustra* alkaloids is an intensely studied area. Individual syntheses were described for (–)-debromoflustramine A, (+)-debromoflustramine A, debromoflustraminol B, and debromoflustrabromine (**2**) with moderate yields. Morales-Ríos et al. and Aburano et al. described efficient routes for the construction of debromodihydroflustramine C (**8**) and debromoflustramide E with overall yields of 39% and 35%, respectively. Debromoflustramine E (**32**) was made *via* four different synthetic routes. The shortest route consisted of 3 steps (24% yield) whereas the longest synthetic sequence required 14 steps with 19% overall yield.

Debromoflustramine B (**51**) is one of the most studied molecules from *F. foliacea* and there are 17 syntheses accounted altogether. Among the eight syntheses of *rac*-debromoflustramine B (**51**), Morales-Ríos et al. prepared **51** on three occasions reaching the highest efficiency of 41% in 6 steps. The most recent synthesis was

48. T. Hino, T. Tanaka, K. Matsuki, M. Nakagawa, *Chem. Pharm. Bull.* **1983**, *31*, 1806–1807.
49. J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *PNAS* **2004**, *101*, 5482–5487.
50. S. Kobayashi, T. Hirano, K. Iwakiri, H. Miyamoto, A. Nakazaki, *Heterocycles* **2009**, *79*, 805.
51. O. R. Suárez-Castillo, M. Sánchez-Zavala, M. Meléndez-Rodríguez, E. Aquino-Torres, M. S. Morales-Ríos, P. Joseph-Nathan, *Heterocycles* **2007**, 71, 1539–1551.
52. N. Hara, S. Nakamura, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 2976–2980.
53. M. S. Morales-Ríos, O. R. Suárez-Castillo, P. Joseph-Nathan, *Tetrahedron* **2002**, *58*, 1479–1484.

reported by Zhou et al., who prepared the *rac*-debromoflustramine E (**32**) in 41% over 10 steps and thus far the best synthesis of **32**. Although Cardoso et al. improved the synthesis of (+)-debromoflustramine B (**51**) from 12 to 10 steps, the best route to **51** in 8 steps and 18% overall yield was reported by Morales-Ríos. Enantiopure (–)-debromoflustramine B (**51**) also attracted much attention and there exist five synthetic routes to the molecule. Some of the best syntheses were developed by Trost et al. and Austin et al. providing (–)-debromoflustramine B (**51**) with isolated yields of 46% and 59%, respectively. Table 2 summarizes the total syntheses of individual debromoflustramines with emphasis on the number of steps and overall yield, placed in a chronological order.

Table 2: Syntheses of debromoflustramines.

| Flustramine | Author | ∑ Steps | Overall Yield (%) |
|---|---|---|---|
| (–)-debromoflustramine A | T. Kawasaki (2008)[42] | 9 | 11 |
| (+)-debromoflustramine A | T. Kawasaki (2008)[42] | 9 | 13 |
| *rac*-debromoflustramide B | J. Jensen (1995)[54] | 2 | 32 |
| | D. Aburano (2007)[47] | 4 | 22 |
| | H. Miyamoto (2007)[55] | 13 | 15 |
| (+)-debromoflustramide B | A. S. Cardoso (2001)[56] | 9 | 3 |
| | A. S. P. Cardoso (2007)[57] | 7 | 4 |
| *rac*-debromoflustramine B | J. Jensen (1995)[54] | 3 | 25 |
| | M. S. Morales-Ríos (2001)[37] | 5 | 16 |
| | G. H. Tan (2003)[58] | 4 | 27 |
| | M. S. Morales-Ríos (2005)[59] | 5, 6 | 38, 41 |
| | H. Miyamoto (2007)[55] | 14 | 19 |
| | A. W. Schammel (2010)[60] | 5 | 27 |
| | Y. Zhou (2012)[61] | 10 | 29 |

54. J. Jensen, U. Anthoni, C. Christophersen, P. H. Nielsen, *Acta Chem. Scand.* **1995**, *49*, 68–71.
55. H. Miyamoto, Y. Okawa, A. Nakazaki, S. Kobayashi, *Tetrahedron Lett.* **2007**, *48*, 1805–1808.
56. A. S. Cardoso, N. Srinivasan, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **2001**, *42*, 6663–6666.
57. A. S. P. Cardoso, M. M. B. Marques, N. Srinivasan, S. Prabhakar, A. M. Lobo, *Tetrahedron* **2007**, *63*, 10211–10225.
58. G. H. Tan, X. Zhu, A. Ganesan, *Org. Lett.* **2003**, *5*, 1801–1803.
59. M. S. Morales-Ríos, E. Rivera-Becerril, P. Joseph-Nathan, *Tetrahedron: Asymmetry* **2005**, *16*, 2493–2499.
60. A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron* **2010**, *66*, 4687–4695.
61. Y. Zhou, Y. Xi, J. Zhao, X. Sheng, S. Zhang, H. Zhang, *Org. Lett.* **2012**, 3116–3119.

| Flustramine | Author | ∑ Steps | Overall Yield (%) |
|---|---|---|---|
| (–)-debromoflustramine B | A. S. Cardoso (2001)[56] | 12 | 2 |
| | J. F. Austin (2004)[49] | 6 | 59 |
| | M. S. Morales-Ríos (2005)[59] | 8 | 18 |
| | A. S. P. Cardoso (2007)[57] | 10 | 1 |
| | B. M. Trost (2011)[43] | 4 | 46 |
| (+)-debromoflustramine B | M. Bruncko (1984)[62] | 12 | 5 |
| | A. S. Cardoso (2001)[56] | 12 | 2 |
| | A. S. P. Cardoso (2007)[57] | 10 | 2 |
| | M. S. Morales-Ríos (2005)[59] | 8 | 18 |
| debromoflustraminol B | O. R. Suárez-Castillo (2006)[63] | 6, 7 | 32, 10 |
| debromodihydroflustramine C | S.Takase (1986)[64] | 9 | 2 |
| | M. S. Morales-Ríos (2002)[53] | 5 | 39 |
| | A. Sabahi (2010)[65] | 7 | 25 |
| *rac*-debromoflustramide E | J. Jensen (1995)[54] | 2 | 24 |
| | D. Aburano (2007)[47] | 3 | 35 |
| *rac*-debromoflustramine E | J. Jensen (1995)[54] | 3 | 24 |
| | M. S. Morales-Ríos (2002)[53] | 5 | 23 |
| | H. Miyamoto (2007)[55] | 14 | 19 |
| | Y. Zhou (2012)[61] | 10 | 41 |
| debromoflustrabromine | I. V. Zhun (2004)[66] | 3 | 34 |

## 2.3 Biological evaluation of flustramines

Even before the isolation of any alkaloids from the bryozoan *F. foliacea*, Al-Ogily and Knight-Jones reported, in 1977, that the larvae of *F. foliacea* readily settled at the distal growing edge of the other bryozoan *Scrupocellaria reptans* to colonize and that the older parts of the fronds showed higher antibacterial activity.[67] They also indicated that the older parts of the fronds emitted the characteristic smell of lemon

62. M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.* **1984**, *59*, 5543–5549.
63. O. R. Suárez-Castillo, M. Sánchez-Zavala, M. Meléndez-Rodríguez, L. E. Castelán-Duarte, M. S. Morales-Ríos, P. Joseph-Nathan, *Tetrahedron* **2006**, *62*, 3040–3051.
64. S. Takase, I. Uchida, H. Tanaka, H. Aoki, *Tetrahedron* **1986**, *42*, 5879–5886.
65. A. Sabahi, J. D. Rainier, *Arkivoc* **2010**, *8*, 116–125.
66. I. V. Zhun, A. V. Ignatenko, *Russ. Chem. Bull.***2004**, *53,* 2221–2223.
67. S. Al-Ogily, E. W. Knight-Jones, *Nature* **1977**, *265*, 728–729.

which is distinct from the growing edges of fronds. The muscle relaxation capability of the *Flustra* extract was partly attributed to flustramine A (**9**).[68]

Later, Wright indicated strong activity of the crude extract of *F. foliacea* against *B. subtilis* although no exact quantification was mentioned.[24] Similarly, the alkaloid fraction containing mainly dihydroflustramine C (**7**), and flustramine D (**47**) showed unspecific activity against *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, *Staphylococcus aureus,* and *Staphylococcus epidermidis*.[69]

At a concentration of 1000 ppm in DMSO, flustramine E (**50**) was inactive against *P. aeruginosa*, *Pythium ultimum*, and *Aspergillus niger*. However, at the same dosage, a marginal activity was observed for *B. subtilis*, *Fusarium oxysporum*, and *Saccharomyces cerevisiae* with complete zones of inhibition in the range of 12, 10, and 14 mm, respectively. Further antimicrobial evaluation of flustramine E (**50**) was made at concentrations of 1000, 100, and 10 ppm, against *Rhizotonia solani* and *Botrytis cinerea*. The complete zones of inhibition for *R. solani* were 10, 9, and 9 mm whereas *B. cinerea* exhibited 27, 25, and 21 mm, respectively.[29]

Other structurally related flustramines isolated from Canadian waters showed strong activity against *B. subtilis* while flustramine E (**50**) isolated from coastal Denmark showed only moderate activity. It could be speculated that the ecological environments in both these areas are substantially different resulting in differential response from the same bryozoan to produce different alkaloids with varied concentrations. This behavior supports the “theory of adaptive variance” as proposed by Christophersen.[70]

Peters, Wright et al. extensively evaluated the 11 isolated secondary metabolites in an agar diffusion assay against marine and non-marine bacteria such as *H. Marina*, *E. coli*, *B. megaterium*, *Roseobacter* sp., *Sulfitobacter* sp., *Pseudomonas pabuli*, and *Psychroserpens* sp. The latter four bacterial strains were obtained from *F. foliacea* itself. Of the 11 tested compounds none was able to inhibit the growth of *H. marina.* The inhibition zones against *E. coli*, *B. megaterium*, and *Roseobacter* sp. were in the

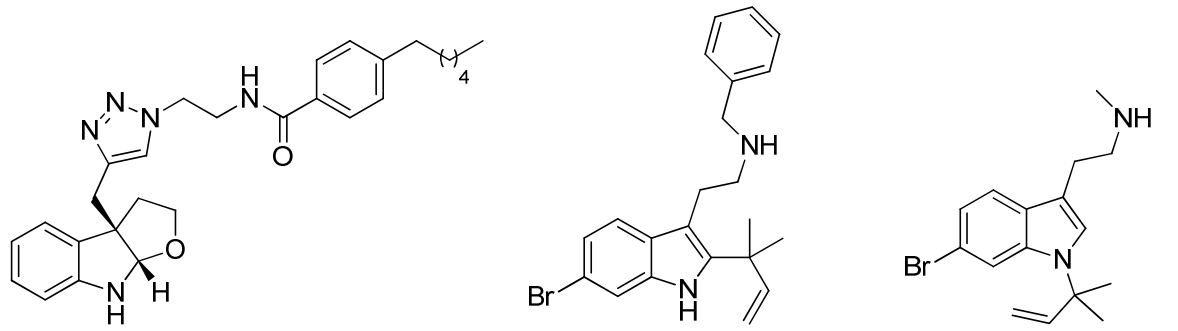
68. T. Sjöblon, L. Bohlin, c. Christophersen, *Acta Pharm. Suec.* **1983**, *20* (6), 415–418.
69. M. V. Laycock, J. L. C. Wright, J. A. Findlay, A. D. Patil, *Can. J. Chem.* **1986**, *64*, 1312–1316.
70. C. Christophersen, *Comp. Biochem. Physiol.* **1991**, *98*, 427–432.

range of 1 to 5 mm (1 mg/mL) while against *P. pabuli* the activities were in the range of 2 to 7 mm. With the exception of a 12 mm inhibition zone for compound **54**, all other compounds showed inhibition zones ranging from 2 to 5 mm against *Psychroserpens* sp. However, moderate activity against *Sulfitobacter* sp. was observed with 2 to 7 mm for complete zones of inhibition for compounds **53**, **54**, **56**, **57**, **3**, and **41**, respectively.

Furthermore, the compounds **3**, **53**, **7**, **41**, and **47** were evaluated for AHL dependent quorum sensing activity. At a concentration of 20 µg/mL, dihydroflustramine C (**7**) caused a reduction in the fluorescent signal intensity of 50% against *P. putida* (pKR-C12) and *E. coli* (pSB403) and of 30% against *P. putida* (pAS-C8). Similarly, flustramine D (**47**) caused reduction in the signal intensity by 50% against *E. coli* (pSB403) and by 20% against both *P. putida* (pKR-C12) and *P. putida* (pAS-C8). These results point at a specific inhibition of AHL-mediated cell-cell communication.[32]

In 2011, Bunders, Melander, et al. synthesized deformylflustrabromine (**3**) and flustramine C (**5**) following the procedures reported by Lindel et al. and screened for a possible bacterial biofilm inhibition. When tested against three different strains of bacterial pathogens, *Acetonetobacter baumannii*, *E. coli*, and methicillin resistant *Staphylococcus aureus* (MRSA), flustramine C (**5**) showed moderate antibiofilm activity (30% at 100 µM).[71] Deformylflustrabromine (**3**) inhibited *E. coli* and *S. aureus* biofilm formation with moderate activity as well ($IC_{50}$ = 174 and 70 µM, respectively).[72] Furthermore, synthetic derivatives of flustramines (Figure 8) were prepared and evaluated for antibiofilm activity resulting in enhanced activities.

71. C. Bunders, J. Cavanagh, C. Melander, *Org. Biomol. Chem.* **2011**, *9*, 5476–5481.
72. C. A. Bunders, M. J. Minvielle, R. J. Worthington, M. Ortiz, J. Cavanagh, C. Melander, *J. Am. Chem. Soc.* **2011**, *133*, 20160–20163.




*S. aureus*, $IC_{50}$ = 19.2 μM
*MRSA*, $IC_{50}$ = 18.7 μM

*S. aureus*, $IC_{50}$ = 5.9 μM
*E. coli*, $IC_{50}$ = 53 μM

*S. aureus,* $IC_{50}$ = 65 μM
*E. coli*, $IC_{50}$ = 80 μM

Figure 8: Antibiofilm active analogues.[71,72]

Lysek, Lindel, et al. reported the cytotoxicity of *Flustra* alkaloids for the first time. Deformylflustrabromine (**3**) showed the highest cytotoxicity against human colon cancer cell line HCT-116 with an $IC_{50}$ value of 5.8 μM while flustramine A (**9**), flustramine D (**47**), and dihydroflustramine C (**7**) showed weak activity in the range of 26 μM.[33]

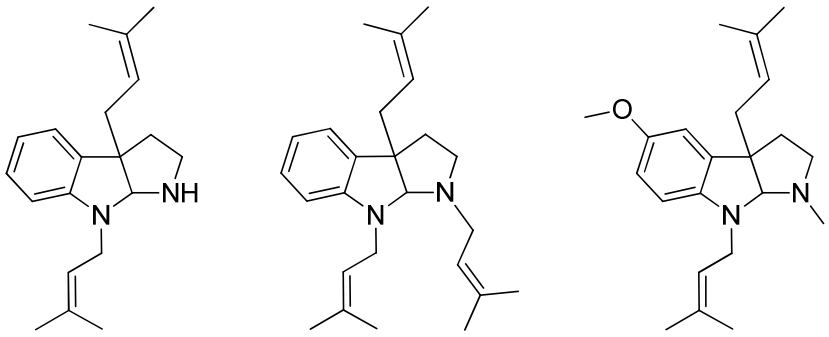
For concentrations up to 10 μM, deformylflustrabromine (**3**), flustramine A (**9**), flustramine C (**5**), and dihydroflustramine C (**7**) showed specific effects neither on evoked currents of the activated potassium channels (Kv1.1 and Kv1.4) nor on the rat brain $Na_v1.2$ sodium channel.[31]

Acetylcholine (ACh) is responsible for the opening of nicotinic acetylcholine receptors (nAChRs). Sala et al. reported that the natural product deformylflustrabromine (**3**) when co-applied with ACh, selectively caused potentiation in α4β2 human neuronal nicotinic acetylcholine receptors. This effect was fast, reversible, and concentration dependent although high concentrations were required.[73] The same result was confirmed again, following experiments on human α7 and α4β2 nACh receptors expressed in *Xenopus* oocytes by Kim, Glennon, et al. They reported that deformylflustrabromine (**3**) and deformylflustrabromine B (**56**) were able to inhibit α7 nACh receptors with $IC_{50}$ values of 44 μM and 14 μM, respectively.[46] Continuing on the same topic, German, Glennon, et al. dis-assembled the natural product deformylflustrabromine (**3**) to prepare synthetic analogues, aiming at determining the structural components responsible for the action against

73. F. Sala, J. Mulet, K. P. Reddy, J. A. Bernal, P. Wikman, L. M. Valor, L. Peters, G. M. König, M. Criado, S. Sala, *Neurosci. Lett.* **2005**, *373*, 144–149.

α7 and α4β2 nACh receptors. Although the natural product **3** was moderately active against α4β2 nACh ($EC_{50}$ = 0.32 μM) and α7 nACh receptors ($pIC_{50}$ = 5.73), the molecule with a hydrogenated *tert*-prenyl group was more selective ($pIC_{50}$ = 6.86).[74] Recently, Pérez, Gündisch, et al. prepared and tested a variety of indole derivatives, including deformylflustrabromine B (**56**) and deformylflustrabromine (**3**), for their affinity towards α4β2, α3β4, α7, and $(α1)_2β2$ nicotinic acetylcholine receptors. The radioligand binding assays indicated that deformylflustrabromine B (**56**) did not increase responses when co-applied with ACh on α4β2 receptors. Instead, **56** inhibited ACh-induced responses in α4β2 and α7 receptors.[75]

Rivera-Becerril, Morales-Ríos, et al. synthesized and tested the analogues of debromoflustramine B (**51**) for *in vitro* cholinesterase inhibition.[76] Against human butyrylcholinesterase (BChE), *rac*-debromoflustramine B (**51**) showed an inhibition with an $IC_{50}$ of 2.6 μM, whereas (–)-debromoflustramine B (**51**) exhibited an elevation in activity ($IC_{50}$ = 1.4 μM). The enantiopure (+)-debromoflustramine B was inactive, but other synthetic derivatives **99**, **100**, and **101** (Figure 9) were found to be more active than the natural products with $IC_{50}$ values of 0.26, 1.72, and 4.59 μM, respectively.




**99** **100** **101**

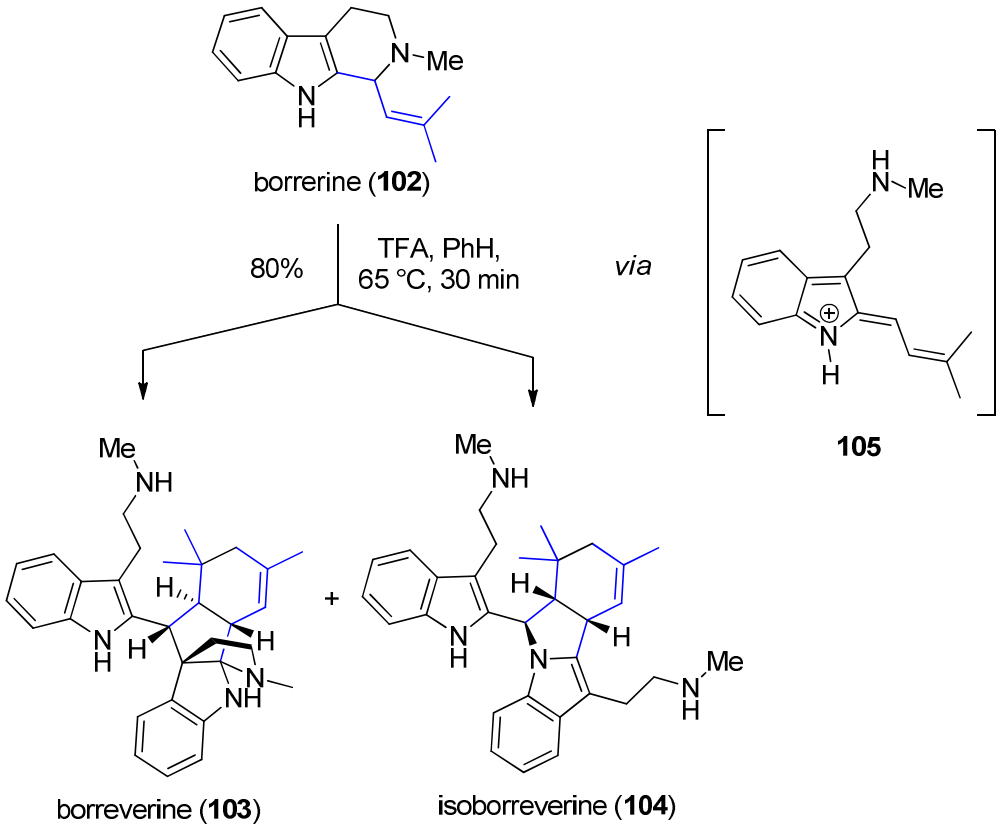
Figure 9: Synthetic analogues of **51** were active on human BChE.[76]

74. N. German, J.-S. Kim, A. Jain, M. Dukat, A. Pandya, Y. Ma, M. Weltzin, M. K. Schulte, R. A. Glennon, *J. Med. Chem.* **2011**, *54*, 7259–7267.
75. E. G. Pérez, B. K. Cassels, C. Eibl, D. Gündisch, *Bioorg. Med. Chem.* **2012**, *20*, 3719–3727.
76. E. Rivera-Becerril, P. Joseph-Nathan, V. M. Pérez-Álvarez, M. S. Morales-Ríos, *J. Med. Chem.* **2008**, *51*, 5271–5284.

*Flustra* alkaloids possess complex structures having distinct functionalities at various positions. They exhibit a wide variety of selectivity against a range of biological targets. It is also very interesting to address the issue of "how nature makes these molecules effectively and converts one natural product into another?" The following section highlights some of the biomimetic postulations with respect to the formation of prenylated indole alkaloids, in general.

## 2.4 Biomimetic syntheses of prenylated indole alkaloids

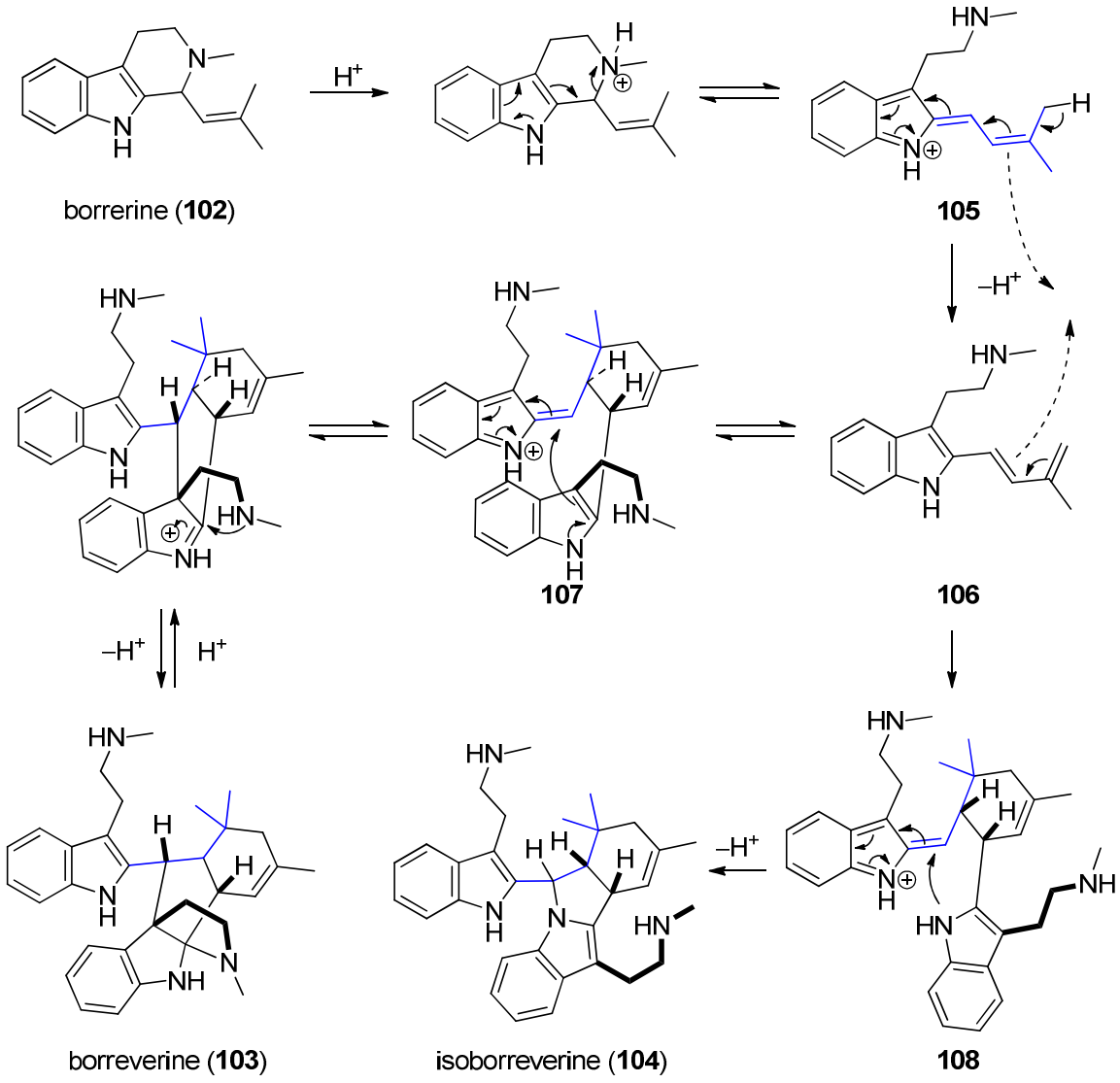
Biomimetic conversion of natural products is highly interesting. One of the earliest examples in the indole alkaloid field was given by Tillequin and Koch who chemically interconverted the natural product borrerine (**102**) to borreverine (**103**) and isoborreverine (**104**) by refluxing in TFA/benzene at 65 °C (Scheme 16).[77]




Scheme 16: Biomimetic conversion of *Borreria* alkaloids.[77]

77. F. Tillequin, M. Koch, J.-L. Pousset, A. Cavé, *J. Chem. Soc., Chem. Commun.* **1978**, 826–828.

The plausible biomimetic dimerization proceeds *via* protonation of borrerine (**102**) to result in two open analogous structures **105** and **106**. The intermolecular cycloaddition *via* two *cis-trans* isomeric forms **107** and **108** would lead to the formation of these natural products (Scheme 17).



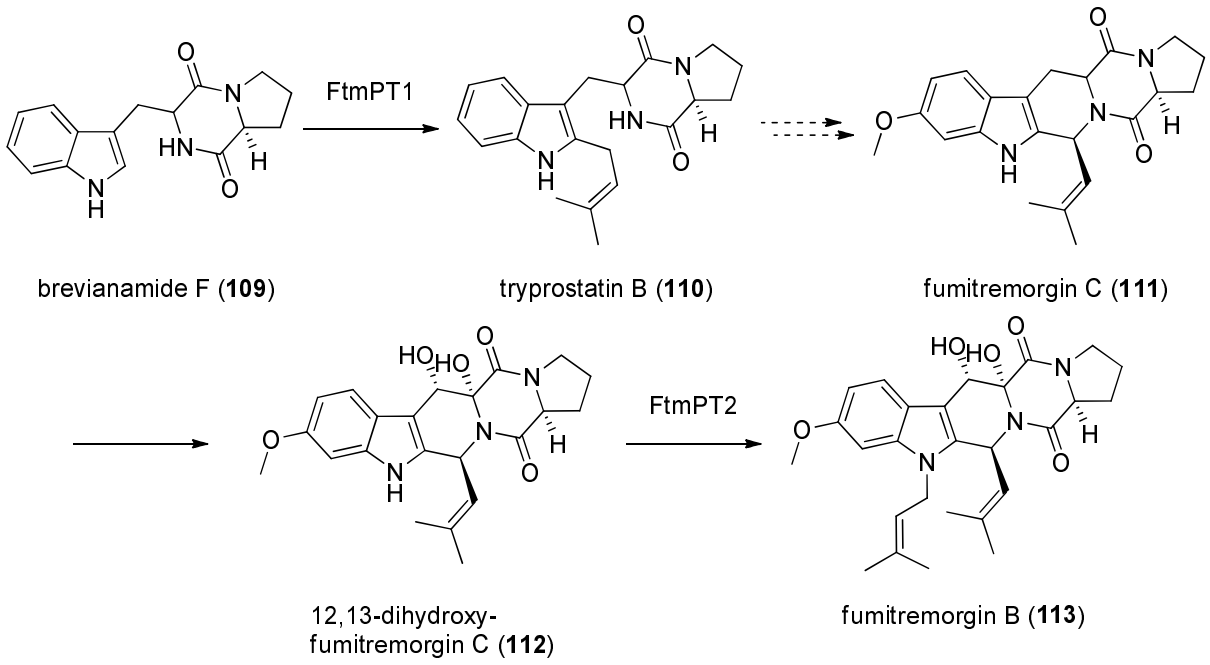

Scheme 17: Postulated biomimetic conversion of borrerine (**102**) to borreverine (**103**) and isoborreverine (**104**).[77]

The extract from aerial parts of the plant *Borreria verticillata* is externally applied for the treatment of skin diseases in West Africa. The indole alkaloids spermacoceine,[78]

78. A. M. Baldé, L. A. Pieters, A. Gergely, V. Wray, M. Claeys, A. J. Vlietinck, *Phytochemistry* **1991**, *30*, 997–1000.

borrerine (**102**) [79] and its dimers borreverine (**103**)[80] and isoborreverine (**104**) [81,82] co-occurred in *B. verticillata*.

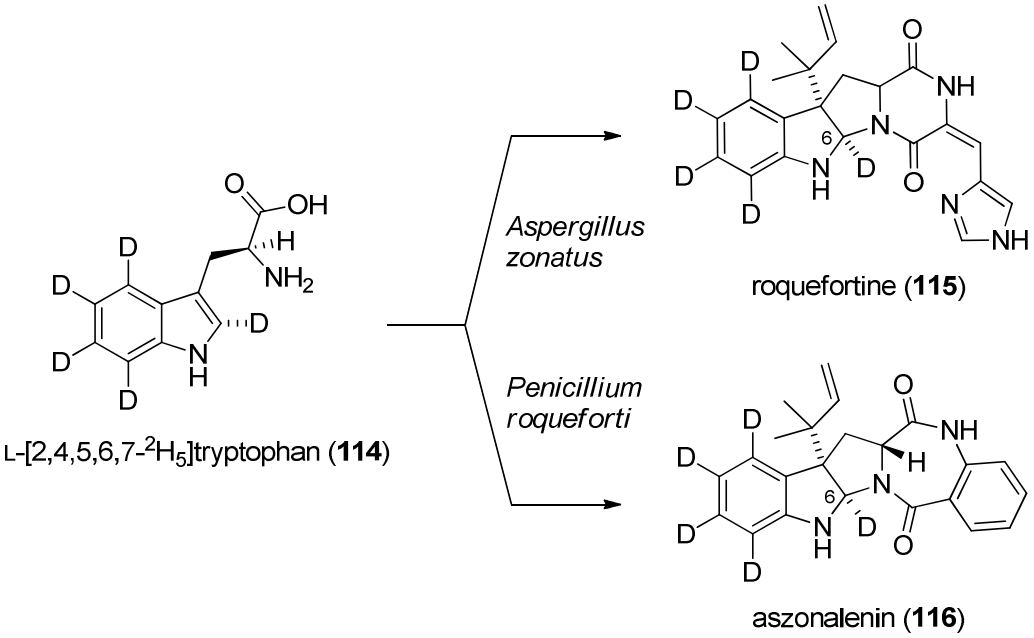
With the aid of biotechnological techniques, Shu-Ming Li made significant contributions in developing biochemical prenylation methodologies. *Aspergillus fumigatus* is a fungal strain from which the prenylated diketopiperazine fumitremorgin B (**113**) was isolated. Grundmann and Li identified the prenyltransferase gene FtmPT1 (fumitremorgin prenyltransferase 1) and showed that this enzyme was able to catalyse the prenylation at indole 2-position of brevianamide F (**109**) to afford tryprostatin B (**110**) in a single biochemical transformation.[83] Later, the *N*-prenyltransferase enzyme FtmPT2 was found to catalyse the *N*-prenylation of indole nitrogen and thus demonstrating the feasibility of the last step in the biosynthesis of fumitremorgin B (**113**, Scheme 18).[84]




Scheme 18: Biosynthesis of tryprostatin B (**110**) and fumitremorgin C (**113**).[83,84]

79. J. L. Pousset, J. Kerharo, G. Maynart, X. Monseur, A. Cavé, R. Goutarel, *Phytochemistry* **1973**, *12*, 2308–2310.
80. J. L. Pousset, A. Cavé, A. Chiaroni, C. Riche, *J. Chem. Soc., Chem. Commun.* **1977**, *8*, 261–262.
81. F. Tillequin, M. Koch, A. Rabaron, *J. Nat. Prod.* **1985**, *48*, 120–123.
82. A. M. Baldé, A. Gergely, L. A. Pieters, M. Claeys, D. A. Vanden Berghe, A. J. Vlietinck, *Planta Med.* **1989**, *55*, 652.
83. A. Grundmann, S.-M. Li, *Microbiology* **2005**, *151*, 2199–2207.
84. A. Grundmann, T. Kuznetsova, S. S. Afiyatullov, S.-M. Li, *ChemBioChem* **2008**, *9*, 2059–2063.

Bhat and co-workers fed deuterium labeled L-[2,4,5,6,7-$^2H_5$]tryptophan to cultures of *Penicillium roqueforti* and *Aspergillus zonatus* and incorporated the entirely labeled tryptophan into roquefortine (**115**) and aszonalenin (**116**), respectively (Scheme 19).[85,86] The deuterium found at C-6 of the resulting natural products stemmed from the labeled L-tryptophan. It was also found that the *tert*-prenyl group in the final natural products had not been transferred *via* the C-2 of the indole precursor. This is in contrast to the proposal of Barrow et al. [87] and Gorst-Allmann et al.[88] They postulated that the Claisen rearrangement of an N-prenyl group would result in a 2-*tert*-prenyl group which in turn undergoes [1,2] rearrangement to provide the C-3 *tert*-prenylated natural products.

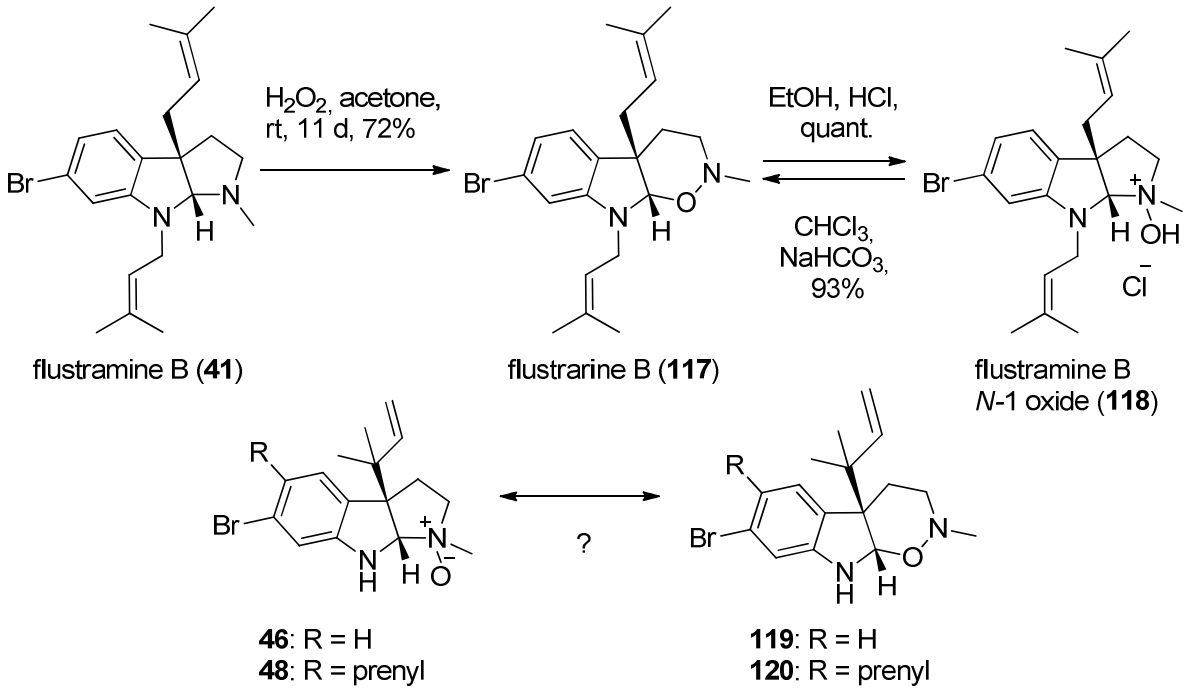



Scheme 19: Incorporation of deuterated tryptophan into roquefortine (**115**) and aszonalenin (**116**).[85,86]

Geneserine and geneseroline were shown to participate in an acid/base catalyzed equilibrium to form physostigmine N-1 oxide and geneseroline N-1 oxide respectively (not shown in Scheme 20).[89] Similarly, Hoist and co-workers reported a reversible facile conversion of flustrarine B (**117**) into flustramine B N-1 oxide hydrochloride

85. B. Bhat, D. M. Harrison, H. M. Lamont, *J. Chem. Soc., Chem. Commun.* **1990**, 1518–1519.
86. B. Bhat, D. M. Harrison, H. M. Lamont, *Tetrahedron* **1993**, *49*, 10663–10668.
87. K. D. Barrow, P. W. Colley, D. E. Tribe, *J. Chem. Soc., Chem. Commun.* **1979**, 225–226.
88. C. P.Gorst-Allman, P. S. Steyn, R. Vleggaar, *J. Chem. Soc., Chem. Commun.* **1982**, 652–653.
89. Q.-S. Yu, H. J. C. Yeh, A. Brossi, J. L. Flippen-Anderson, *J. Nat. Prod.* **1989**, *52*, 332–336.

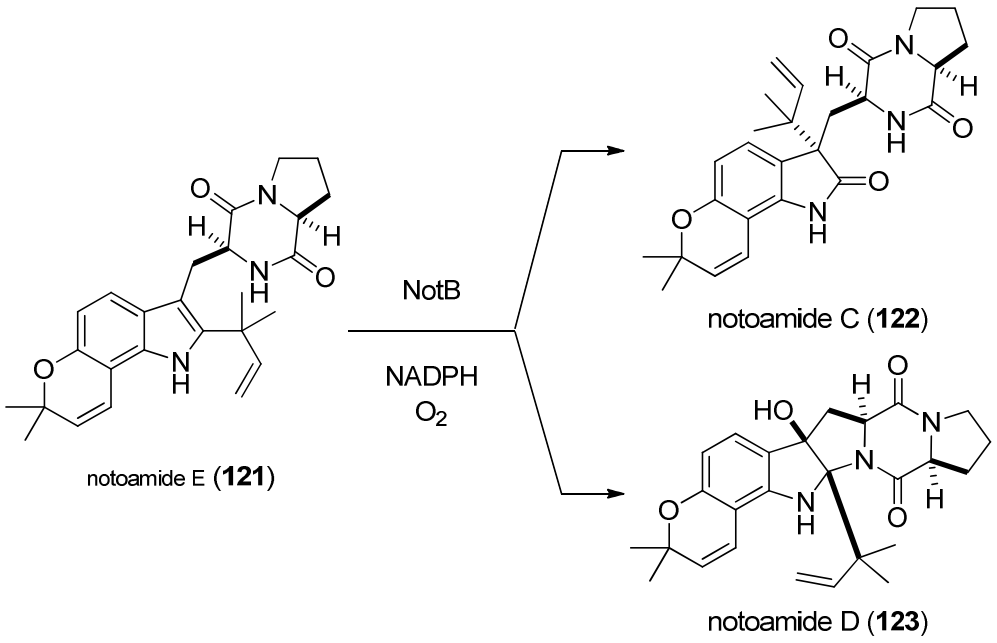
(**118**) in a quantitative manner.[90] On treatment of flustrarine B (**117**) with ethanolic hydrogen chloride, isomeric flustramine B N-1 oxide (**118**) was formed by means of ring contraction. This reaction proved to be reversible under alkaline conditions resulting in the formation of indole **117**. Based on these results, it was proposed that dihydroflustramine C N-oxide (**46**) and flustramine D N-oxide (**48**) isolated from the Canadian collection of *F. foliacea* could exist as hexahydro-1,2-oxazino[5,6-*b*]indole regioisomers **119** and **120** (Scheme 20).




Scheme 20: Interconversion of flustrarines and flustramines.[90]

Recently, Finefield et al. and Li et al. reported the *in vitro* characterization of a FAD dependent monooxygenase NotB (notoamide B prenyltransferase). NotB was utilized for the biomimetic conversion of notoamide E (**121**) into notoamide C (**122**) and notoamide D (**123**), in a ratio of 1:16 (Scheme 21).[91]

90. P. B. Holst, U. Anthoni, C. Christophersen, P. H. Nielsen, *J. Nat. Prod.* **1994**, *57*, 1310–1312.
91. (a) J. M. Finefield, T. J. Greshock, D. H. Sherman, S. Tsukamoto, R. M. Williams, *Tetrahedron Lett.* **2011**, *52*, 1987–1989. (b) S. Li, J. M. Finefield, J. D. Sunderhaus, T. J. McAfoos, R. M. Williams, D. H. Sherman, *J. Am. Chem. Soc.* **2012**, *134*, 788–791.




Scheme 21: Notoamide E (**121**) can be enzymatically converted to notoamide C (**122**) and D (**123**).[91]

# 3 Results and discussion

The chemical synthesis of the natural products $N_b$-formyl-$N_b$-methyltryptamine (**131**), flustrabromine (**1**), deformylflustrabromine (**3**), flustramine A (**9**), flustramine C (**5**), dihydroflustramine C (**7**), and flustramine E (**50**) and the enantioselective synthesis of flustramine C (**5**) was undertaken in this thesis work. Subsequently, the biological activity of the synthesized natural products and their derivatives was assessed against different biological targets.

## 3.1 Synthesis of flustrabromine

Flustrabromine (**1**) is an important intermediate towards the total synthesis of pyrrolo[2,3-*b*]indole alkaloids such as flustramine A (**9**), flustramine C (**5**), and dihydroflustramine C (**7**). Retrosynthetic analysis of this natural product would result in known indole alkaloids such as $N_b$-formyl-$N_b$-methyltryptamine (**131**) $N_b$-methyltryptamine (**126**) and commercially available tryptamine (**124**). A stepwise introduction of the structural features is crucial for the total synthesis of this natural product. For the synthesis of flustrabromine (**1**), an efficient methodology was adopted that has been developed by Bräuchle.[92].

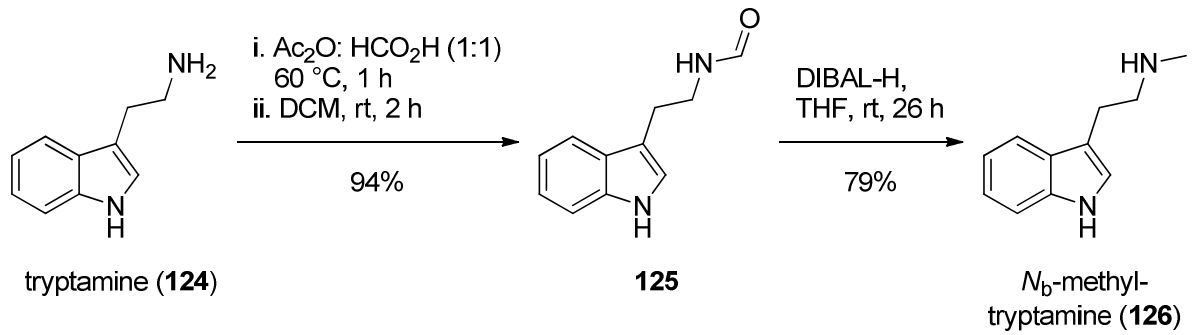
### 3.1.1 Synthesis of $N_b$-formyl-$N_b$-methyltryptamine (131)

The initial target was to introduce a methyl group onto the amino group of the aliphatic side chain of tryptamine (**124**). This methyl group can serve as a protecting group at the initial stages as well as a methyl substituent of the pyrrolo[2,3-*b*]indole natural products **5**, **7**, **9**, and **32** at the later stages. Efficient methylation can be achieved by formylation of the primary amino group, followed by reduction with DIBAL-H.

For the formylation of tryptamine (**124**), the protocol by Bosch was used.[93] A mixture of $Ac_2O$ and $HCO_2H$ was stirred at 60 °C for 1 h. A solution of tryptamine (**124**) in DCM was added to this acid mixture and stirred for 2 h at room temperature affording the formamide **125** in an excellent yield of 94%. Without any further

92. L. Bräuchle, *Dissertation* **2005**, Ludwig-Maximilians-Universität München.
93. J. Bosch, T. Roca, M. Armengol, D. Fernandez-Forner, *Tetrahedron* **2001**, *57*, 1041–1048.

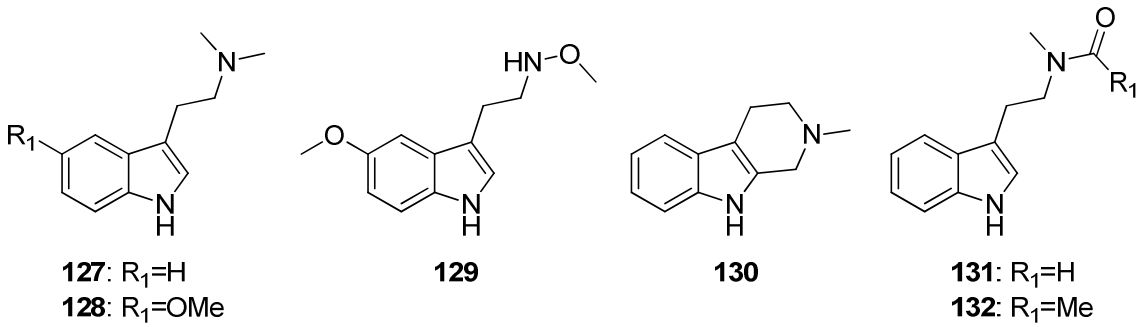
purification, the formamide **125** was reduced with DIBAL-H (4.4 equivalents) to form the natural product $N_b$-methyltryptamine (**126**, 74% in two steps (Scheme 22).




Scheme 22: Two step synthesis of $N_b$-methyltryptamine (**126**)

$N_b$-Methyltryptamine (**126**) is also a natural product isolated from a wide variety of Amazonian plants. The flowering shoots and barks of *Virola theiodora*, as well as the leaves of *V. rufula* and *V. calophylla* yielded natural product **126**.[94]

The plant bark of *Virola sebifera* is extensively used for the preparation of hallucinogenic snuffs and drinks in Venezuela. The major chemical components identified from the roots and bark of the plant *V. sebifera* were *N*,*N*-dimethyltryptamine (**127**), 5-methoxy-*N*,*N*-dimethyltryptamine (**128**), 5-methoxy-*N*-methoxytryptamine (**129**), 2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**130**),[94,95] along with $N_b$-formyl-$N_b$-methyltryptamine (**131**) and $N_b$-acetyl-$N_b$-methyltryptamine (**132**, Figure 10).[96] The latter two natural products are present in the form of *E and Z* rotamers in NMR spectroscopy (either in $CDCl_3$ or $C_6D_6$).




**127**: $R_1$=H
**128**: $R_1$=OMe

**129**

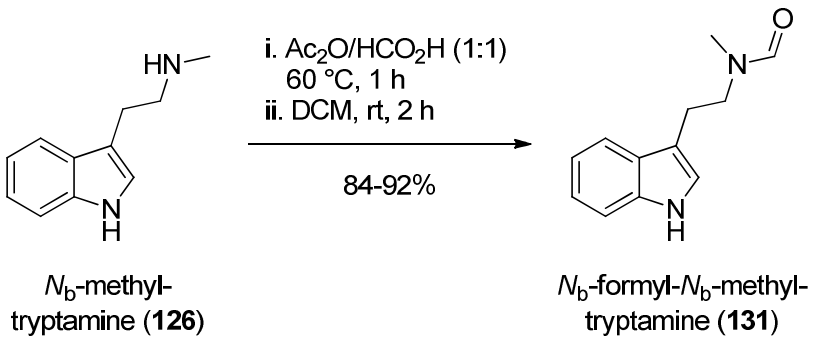
**130**

**131**: $R_1$=H
**132**: $R_1$=Me

Figure 10: Chemical components isolated from *Virola sebifera*

94. S. Agurell, B. Holmstedt, J. E. Lindgren, R. E. Schultes, *Acta. Chem. Scand.*, **1969**, *23*, 903–916.
95. E. Corothie, T. Nakano, *Planta Medica*, **1969**, *17*, 184–188.
96. K. Kawanishi, Y. Uhara, Y. Hashimoto, *Phytochemistry* **1985**, *24*, 1373–1375.

Following Bosch[93] conditions for the second time, **126** was exposed to the pre-heated acidic mixture of $Ac_2O$ and $HCO_2H$ (1:1) to result in smooth transformation of the natural product **131** with a yield ranging between 84-92% (Scheme 23).




Scheme 23: One pot conversion of **126** to $N_b$-formyl-$N_b$-methyltryptamine (**131**).

The hindered rotation around the C-N bond of the amide functional group makes the natural product to exist as two rotational isomers (Figure 11). These two rotamers are present in *Z* and *E* forms, the latter form being the major contributor. In the $^1H$ NMR and $^{13}C$ NMR spectra ($CDCl_3$), all signals are duplicated.

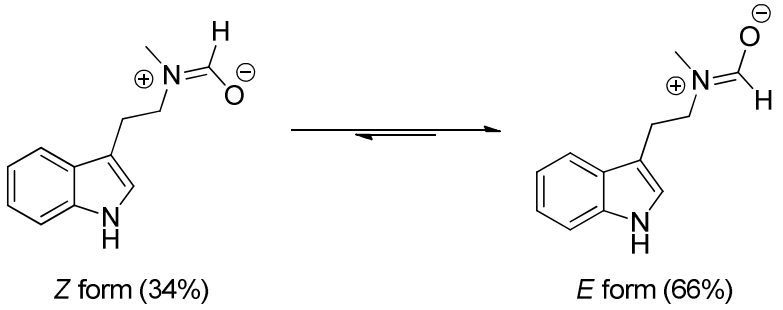
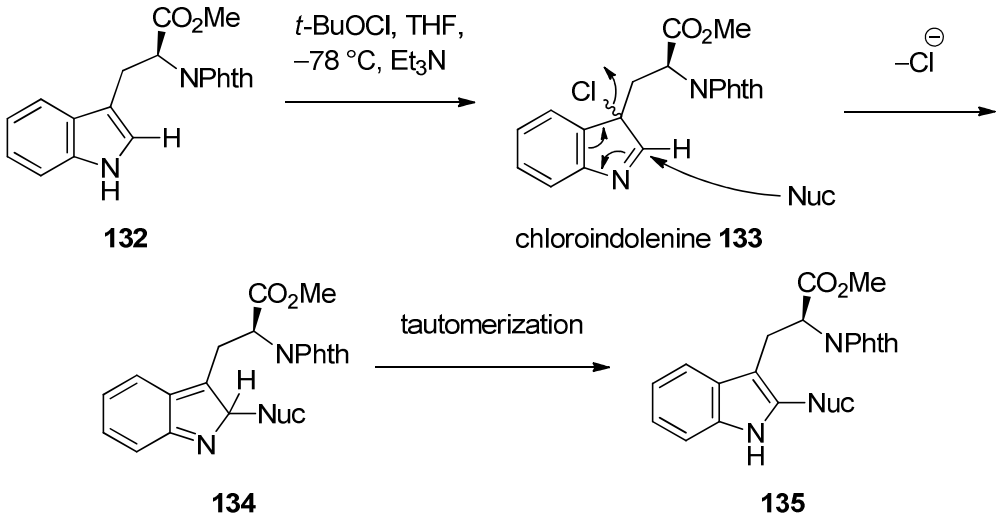



Figure 11: $N_b$-formyl-$N_b$-methyltryptamine (1**31**) exists as two rotational isomers at room temperature (either in $CDCl_3$ or $C_6D_6$).

The structurally related natural product 6-bromo-$N_b$-formyl-$N_b$-methyltryptamine (**45**), isolated from *F. foliacea*, could also serve as a possible precursor for the natural product flustrabromine (**1**).[26] *Tert*-prenylation at the indole C-2 of **45** may result in flustrabromine (**1**) in one step. However, the preparation of the 6-brominated natural product might require a longer sequence. Therefore, 2-*tert*-prenylation followed by bromination on $N_b$-formyl-$N_b$-methyltryptamine (**131**) was chosen for further transformations.

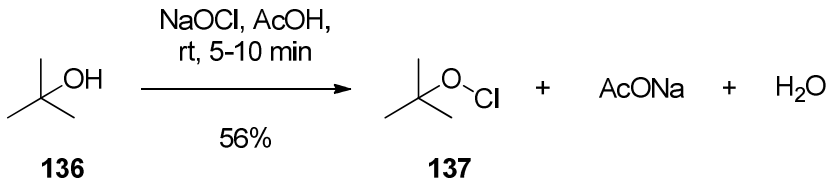
### 3.1.2 *Tert*-Prenylation at the indole C-2

Danishefsky et al. discovered a one step procedure for introducing the entire 1,1-dimethylallyl group.[97] Reaction of 3-substituted indole **132** with *tert*-BuOCl at –78 °C, in presence of $Et_3N$, generates a transient chloroindolenine species **133**. This chloroindolenine **133** is highly electrophilic at the indole 2-position and, hence, readily attacked by an incoming nucleophile. With a suitable nucleophile it is a straight forward approach for the functionalization of indole 2-position with a *tert*-prenyl group (Scheme 24).




Scheme 24: Mechanism of Danishefsky's *tert*-prenylation of the indole 2-position.[97]

To apply Danishefsky's protocol, the reagents *tert*-BuOCl (**137**) and prenyl-9-BBN (**142**) were prepared according to the literature procedures. Reaction of *tert*-Butanol (**136**) with commercially available NaOCl and AcOH at room temperature for 5-10 min furnished the *tert*-BuOCl (**137**) as light sensitive yellow oil (56%, Scheme 25).[98]

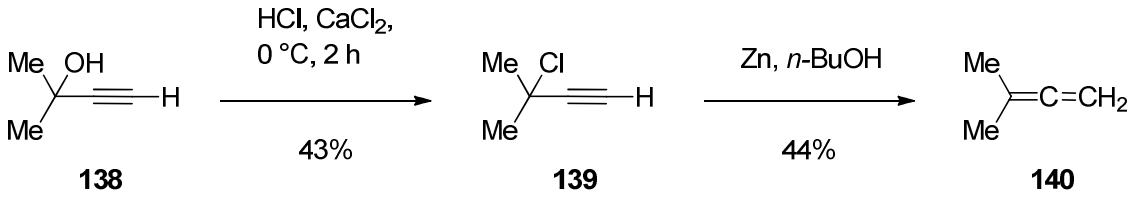



Scheme 25: Synthesis of *tert*-butylhypochlorite (**137**).[98]

The prenyl moiety of the prenyl-9-BBN (**142**) arose from 3-methyl-1,2-butadiene (**140**) which was prepared in two steps. The reaction of propargylalcohol **138** with concentrated HCl in presence of $CaCl_2$ resulted in propargylchloride (**139**). The

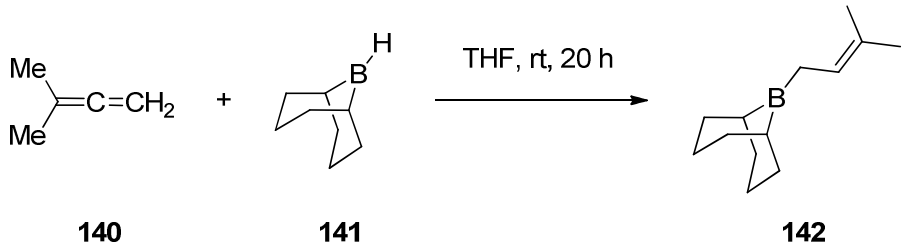
97. J. M. Schkeryantz, J. C. G. Woo, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 7025–7026.
98. M. J. Mintz, C. Walling, *Org. Synth.* **1969**, *49*, 9.

propargylchloride (**139**) in butanol gave the low boiling colorless allene **140** on reaction with metallic Zn powder (19% over two steps (Scheme 26). [99,100]




Scheme 26: Allene **140** was synthesized in two steps.[99,100]

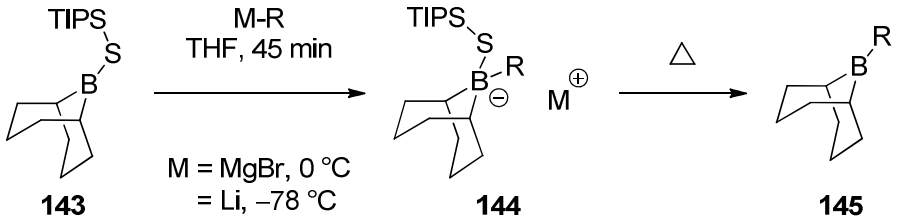
9-BBN-H (9-borabicyclo[3.3.1]nonane, **141**) is an unusually stable hydroboration reagent and was discovered by Brown et al.[101,102,103] Following anti-Markovnikov's rule, 9-BBN-H boronates the least hindered site of the diene system.[104] As a result, reaction of 9-BBN-H (**141**) with 3-methyl-1,2-butadiene (**140**) at room temperature and inert atmosphere gave almost exclusively 3,3-dimethylallyl-9-BBN (**142**, Scheme 27).




Scheme 27: *In situ* preparation of prenyl-9-BBN (**142**).

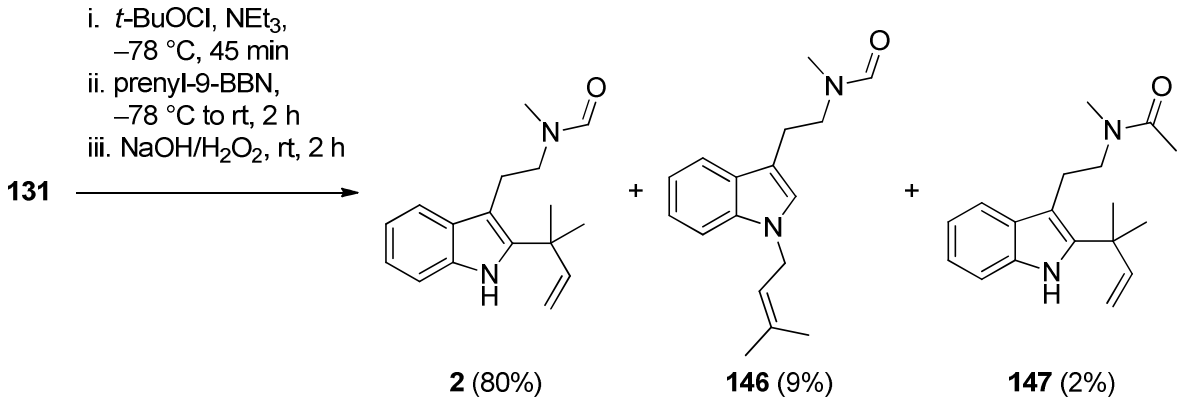
Another synthetic route to prepare alkylated boranes was presented by Soderquist et al.[105] Organolithium or organomagnesium reagents were added to (TIPS)S-9-BBN (**143**) to form "ate" complexes **144** which thermally collapsed to form organoboranes (**145**) in yields above 85% after distillation (Scheme 28).

99. H. Mayr, I. K. Halberstadt-Kausch, *Chem. Ber.* **1982**, *115*, 3479–3515.
100. J. Chengebroyen, M. Linke, M. Robitzer, C. Sirlin, M. Pfeffer, *J. Organomet. Chem.* **2003**, *687*,313-321.
101. E. F. Knights, H. C. Brown, *J. Am. Chem. Soc.* **1968**, *90*, 5280–5281.
102. E. F. Knights, H. C. Brown, *J. Am. Chem. Soc.* **1968**, *90*, 5281–5283.
103. H. C. Brown, A. K. Mandal, *J. Org. Chem.* **1992**, *57*, 4976–4986.
104. G. W. Kramer, H. C. Brown, *J. Organomet. Chem.* **1977**, *132*, 9–27.
105. J. A. Soderquist, J. C. J. de Pomar, *Tetrahedron Lett.* **2000**, *41*, 3537–3539.




Scheme 28: Soderquist et al. showed an alternative preparation of alkylboranes.[105]

$N_b$-Formyl-$N_b$-methyltryptamine (**131**) in THF was reacted with *tert*-BuOCl at –78 °C, in presence of $Et_3N$, for 45 min to generate the chloroindolenine *in situ*. The chloroindolenine was treated with prenyl-9-BBN to affect the 2-*tert*-prenylation. Along with the desired product debromoflustrabromine (**2**, 80%), N-prenylated product **146** (9%), and acetylated indole **147** (2%) were also found in minor amounts (Scheme 29). Formation of **147** was attributed to the presence of trace amounts of $N_b$-acetyl-$N_b$-methyltryptamine (**132**) from the previous step.




Scheme 29: *Tert*-prenylation on $N_b$-formyl-$N_b$-methyltryptamine (**131**).

X-ray crystallography unambiguously proved the structure of the major compound **2**. Interestingly, compound **2** occurred in two independent forms in a single crystal (Figure 12).

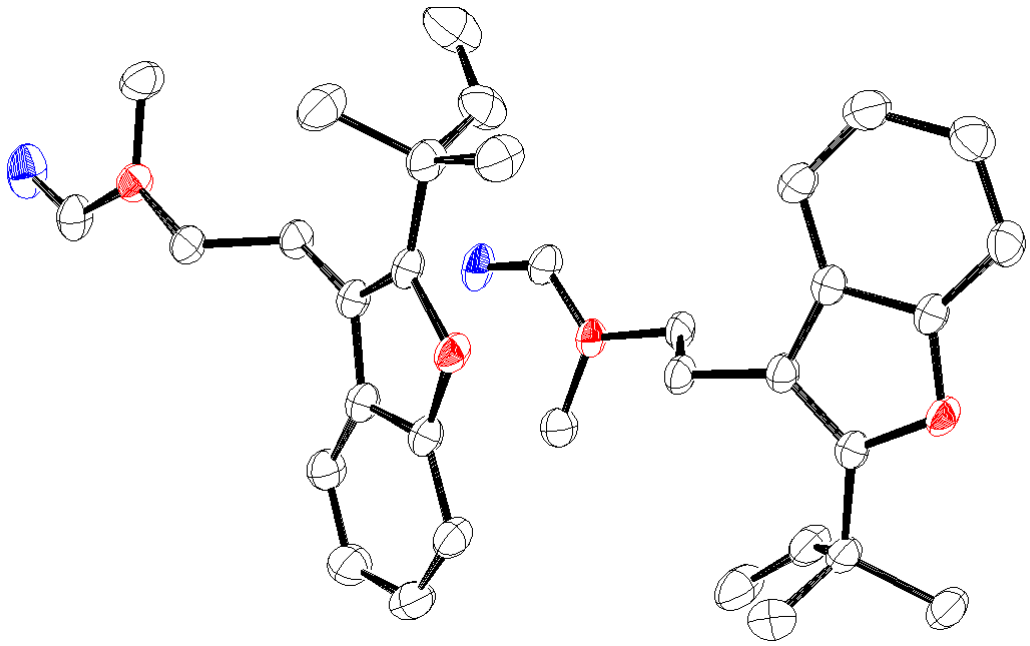


Figure 12: ORTEP drawings of two independent forms of debromoflustrabromine (**2**); hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

Alternative to Danishefsky's procedure of introducing nucleophiles at the indole 2-position, Gribble et al.[106] and Fukuyama et al.[107] reported alkylation of the indole 2-position. Suitably N-1 protected indoles dissolved in THF were reacted with LDA at –100 °C to generate 2-lithiated indoles which were quenched with alkylhalides to result in selective alkylation at the indole C-2 with moderate yields.

### 3.1.3 Completion of flustrabromine (1) synthesis

To determine the existence of rotamers, a variable-temperature NMR experiment at 35 °C and 50 °C was carried out. Coalescence of the signals began to occur at 50 °C despite compound **1** being unstable at higher temperatures.[25]

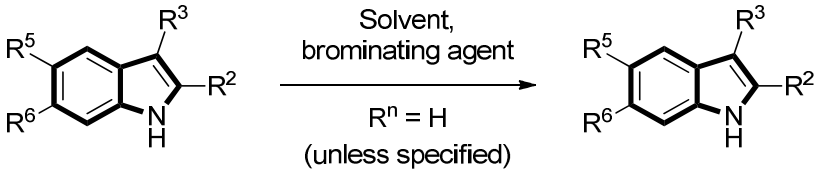
The isolation of debromoflustramine B (**51**) and flustramine B (**41**) from the same extract of *F. foliacea* suggested that bromination might be the last step in the

106. (a) M. G. Saulnier, G. W. Gribble, *J. Org. Chem.* **1982**, *47*, 757–761. (b). Y. Liu, G. W. Gribble, *Tetrahedron Lett.* **2001**, *42*, 2949–2951.
107. T. Fukuyama, X. Chen, G. Peng, *J. Am. Chem. Soc.* **1994**, *116*, 3127–3128.

biosynthesis of flustramine B (**41**).[29] Keeping this in mind, bromination was performed as the last step of the synthesis.

Table 3 highlights a few examples on the bromination/chlorination patterns of indoles with emphasis on halogenating agents, solvents, and selectivities. In most cases, monobromination on indole was achieved using 1 equivalent of the bromine source. In acidic media, indoles prefer bromination at 2-position while the 3, 5, and 6 positions were preferred under slightly basic or neutral conditions. Among the 5 and 6-positions the 5-position is favored. Excess of brominating reagent always resulted in multi bromination (Table 3).

Table 3: Regioselective halogenation on indole.



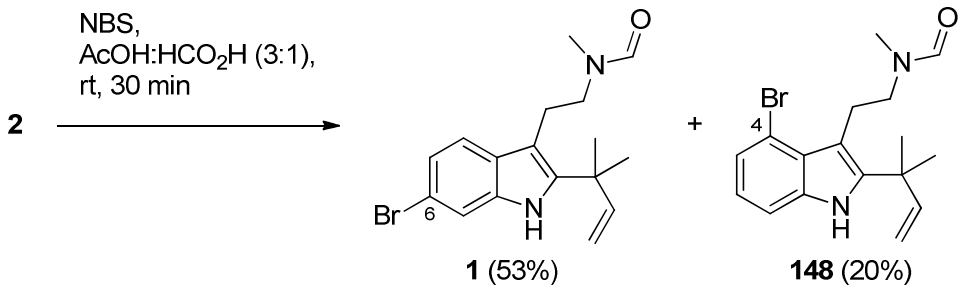

| Halogen Source | Solvent | Starting Material | Product | Priority | Ref. |
|---|---|---|---|---|---|
| NCS (1 eq.) | acetic acid + formic acid | $R^3$= aminoethyl | $R^2$ = Cl (70%) | 2 | 108 |
| NBS (1 eq.) | DCM + Silica / $CCl_4$ | $R^3$ = $CH_2CN$ / Me | $R^2$ = Br (90% / 86%) | 2 | 109 |
| NBS (2 eq.) | aq. t-BuOH | $R^3$ = CHO | $R^{3,3}$ = Br, $R^2$ = oxo (43%) | 3 | 110 |
| $Br_2$ | $Et_3N$ | $R^{2,3}$ = Me | $R^3$ = Br | 3 | 111 |
| NBS (1 eq.) | aq. t-BuOH + $H_2O$ (5%) | $R^3$ = alkyl | $R^5$ = Br, oxindole | 5 | 112 |
| NBS (1 eq.) | aq. t-BuOH | $R^2$=Br, $R^3$= Me | $R^{2,6}$ = Br, $R^3$= Me | 6 | 112 |
| NBS (2 eq.) | DCM + Silica | $R^3$ = $CH_2CN$ | $R^{2,6}$ = Br (95%) | 2,6 | 109 |
| NBS (2 eq.) | DCM + Silica | $R^2$ = Me | $R^{3,6}$ = Br (95%) | 3,6 | 109 |
| NBS (3 eq.) | aq. *t*-BuOH | $R^{4,7}$ = OMe | $R^{3,3,5}$ = Br | 3,3,5 | 110 |
| $Br_2$ (1 eq.) | acetic anhydride | $R^1$ = Me, $R^3$ = glyoxylate | $R^5$ = Br & $R^6$ = Br (7:3) | 5 > 6 | 113f |
| $Br_2$ (1.5 eq.) | acetic acid | $R^1$ = Me, $R^3$ = CHO | $R^5$ = Br (17%) & $R^{3,3,5}$ = Br (7%) | 5 > 3,3,5 | 113 |
| NBS (2 eq.) | acetic acid + | $R^3$= aminoethyl | $R^{2,5}$ = Br & $R^{2,6}$ = Br | 2,5 > 2,6 | 114 |


108. F. Y. Miyake, K. Yukushijin, D. A. Horne, *Org. Lett.* **2004**, *6*, 711–713.
109. A. G. Mistry, K. Smith, M. R. Bye, *Tetrahedron Lett.* **1986**, *27*, 1051–1054.
110. J. Parrick, A. Yahya, A. S. Ijaz, J. Yizun, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2009–2015.
111. E. A. Gross, S. F. Vice, G. I. Dmitrienko, *Can. J. Chem.* **1981**, *59*, 635–640.
112. R. L. Hinman, C. P. Bauman, *J. Org. Chem.* **1960**, *29*, 1206–1215.
113. A. D. Settimo, E. Nannipieri, *J. Org. Chem.* **1970**, *35*, 2546–2551.
114. F. Y. Miyake, K. Yakushijin, D. A. Horne, *Org. Lett.* **2004**, *6*, 4249–4251.

| Halogen Source | Solvent | Starting Material | Product | Priority | Ref. |
|---|---|---|---|---|---|
| | formic acid | | (4:3) | | |
| $Br_2$ (5 eq.) | acetic acid | $R^1$ = Me | $R^{2,3,5,6}$ = Br (major) & $R^{3,3,5,6}$= Br (minor) | 2,3,5,6 > 3,3,5,6 | 113 |

Horne et al.[114] showed that 2 equivalents of NBS in presence of AcOH and $HCO_2H$ react with indole to furnish dibrominated compounds in a ratio of 4:3 with a priority of 2,5-dibrominated compounds over 2,6-dibrominated adducts. Under similar conditions, debromoflustrabromine (**2**) was reacted in a mixture of AcOH and $HCO_2H$ with 1.1 equivalents of NBS at room temperature. 6-Bromination dominated **1** (53%) over formation of the 4-bromo regioisomer **148** (20%, Scheme 30). Probably, the indole 3-position is protonated[115] in AcOH-$HCO_2H$ (3:1) affording the indoleninium ion. $S_EAr$ reaction will be favored at the indole 4- and 6-positions which are located at the *meta*-positions with respect to the iminium nitrogen and in the *ortho*- and *para*-positions of the indole-3-positon.

There are distinct differences between both regioisomers. In the $^1H$ NMR spectrum of **1** ($CDCl_3$) a doublet with a large coupling constant ($J$ = 8.4 Hz) was observed for each of the rotamers (δ = 7.29, 7.49 ppm, respectively). This doublet coupled with C-3 (δ = 107.1, 108.0, respectively) in the HMBC experiment whereas the doublets with small coupling constant ($J$ = 1.6 Hz, 7-H) did not couple with C-3. A melting point of 218 °C was observed for flustrabromine (**1**) whereas isoflustrabromine (**148**) degraded above 155 °C.




**1** (53%) **148** (20%)

Scheme 30: Regioselective bromination afforded flustrabromine (**1**).

Until now, no bromination of the benzene part of indole was reported in THF. When the bromination reaction was performed in THF, flustrabromine (**1**) precipitated in the

115. V. A. Budylin, L. G. Yudin, A. N. Kost. *Khim. Geterotsikl. Soedin.* **1980**, 1181–1199.

reaction flask in low yield (32%), although other compounds formed in this reaction were not characterized. X-ray crystallography confirmed the presence of bromine at 6-position of flustrabromine (**1**, Figure 13). All the other analytical data were in full agreement with the published information.

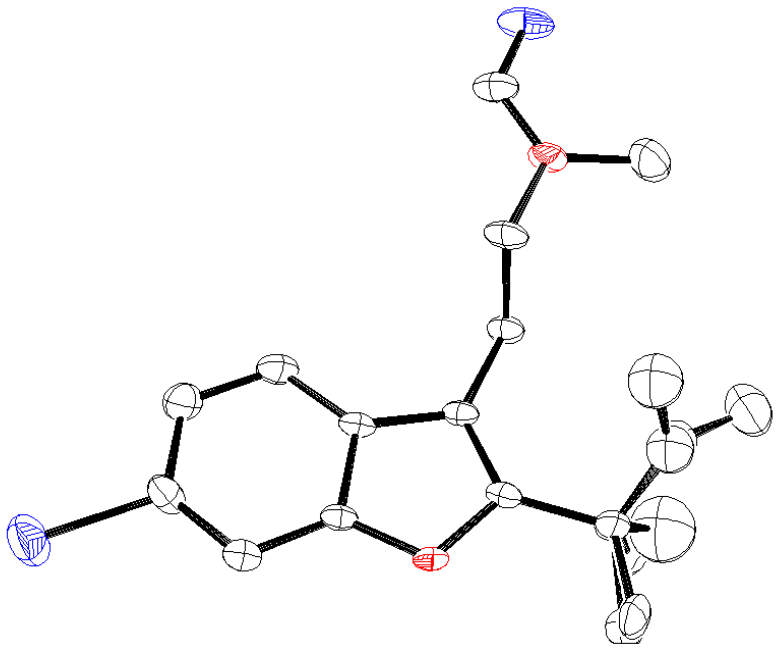


Figure 13: ORTEP drawing of flustrabromine (**1**); hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

## 3.2 Synthesis of flustramine C

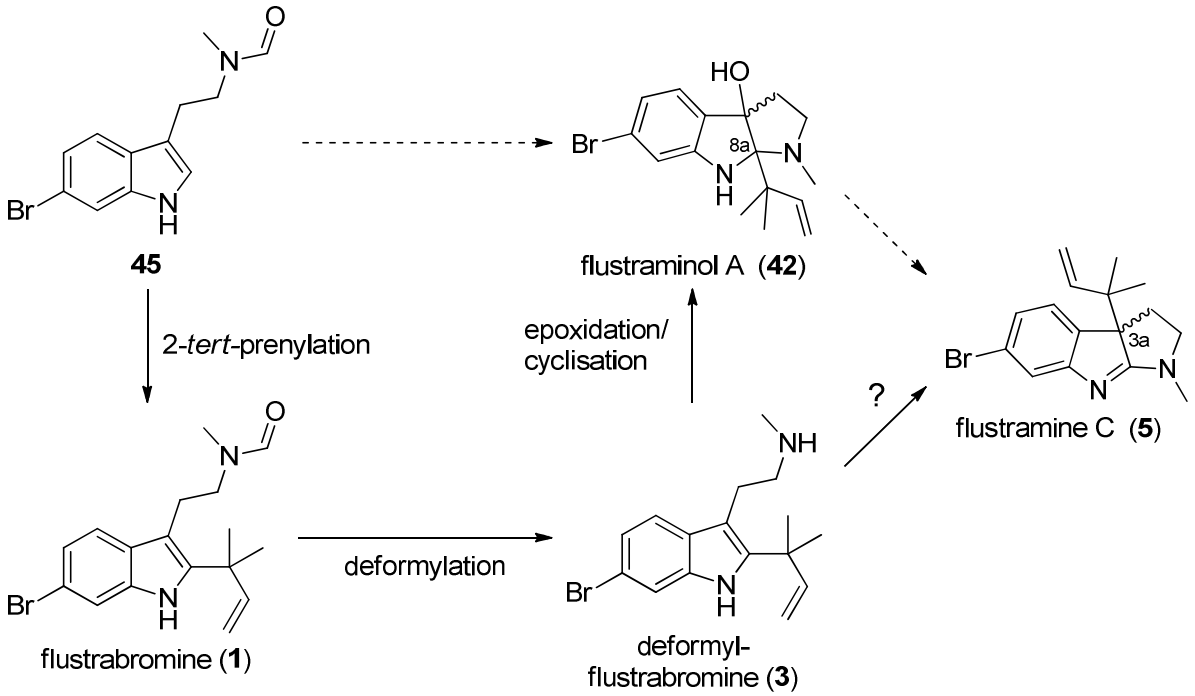
The pyrrolo[2,3-*b*]indole flustramine C (**5**) was isolated by Carlé and Christophersen. For the chemical synthesis of flustramine C (**5**), the synthetic route developed by Lindel et al. was adopted. [116]

### 3.2.1 Synthesis of deformylflustrabromine (3)

The name was derived from flustrabromine (**1**) as the isolated **3** is lacking the formyl group.[33] Peters et al. independently described the isolation of deformylflustrabromine (**3**).[31]

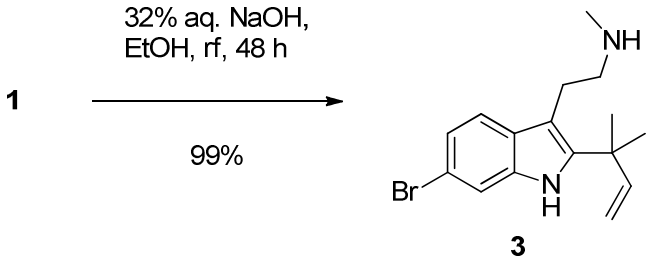
116. T. Lindel, L. Bräuchle, G. Golz, P. Böhrer. *Org. Lett.* **2007**, *9*, 283–286.

Lysek et al. proposed that the deformylflustrabromine (**3**) represents the missing link between other isolated members of *F. foliacea* such as flustrabromine (**1**) and flustraminol A (**42**).[33] Flustraminol A (**42**) with its tricyclic pyrrolo[2,3-*b*]indole core may serve as a starting point for flustramine C (**5**) and dihydroflustramine C (**7**) derivatives as well (Scheme 31). To prove the above hypothesis, the conversion of the natural product flustrabromine (**1**) to deformylflustrabromine (**3**) was attempted. Flustrabromine (**1**) was dissolved in EtOH and refluxed in presence of 32% aqueous NaOH for two days to undergo deformylation. The natural product **3** was obtained in almost quantitative yield (Scheme 32).




Scheme 31: Deformylflustrabromine (**3**) as the missing link between flustramines.[33,116]

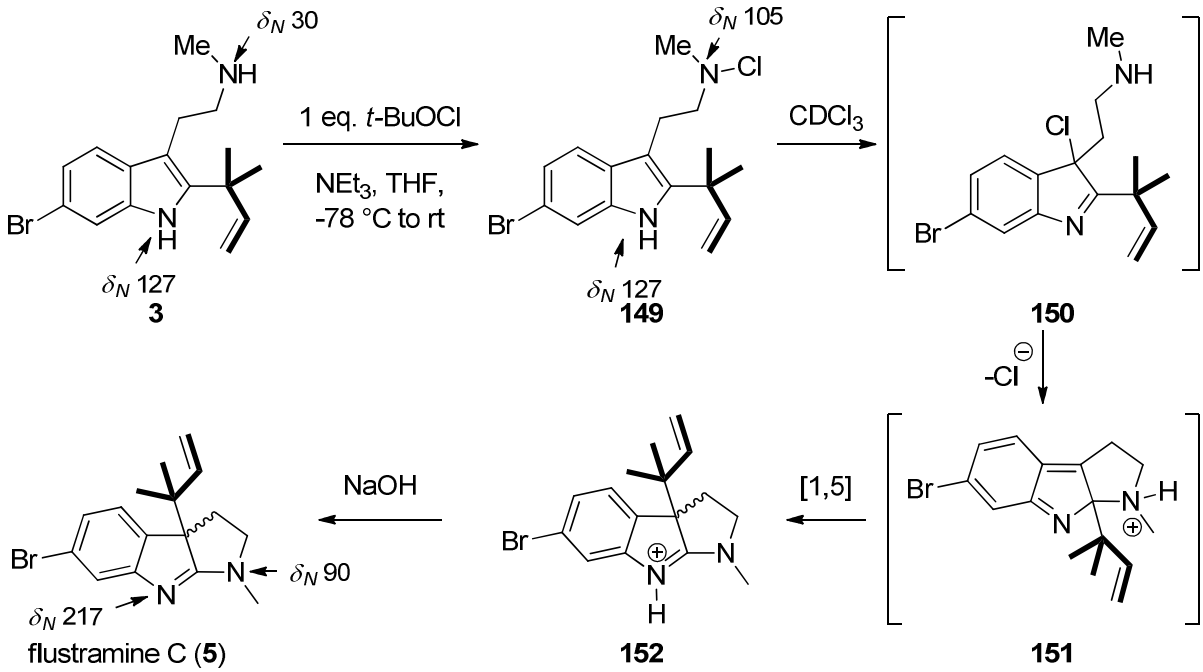
Thus far, this was the best chemical route to obtain **3** from the commercially available tryptamine (**124**) in 6 steps with an overall yield of 27%.




Scheme 32: Conversion of flustrabromine (**1**) to deformylflustrabromine (**3**).

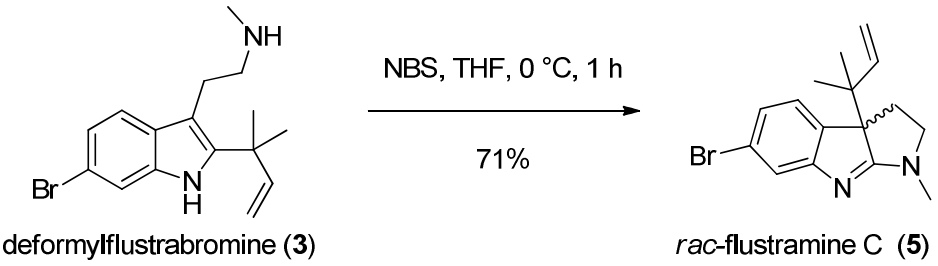
### 3.2.2 Biomimetic preparation of flustramine C (5)

Lindel et al. discovered the key biomimetic transformation of deformylflustrabromine (**3**) to flustramine C (**5**).[116] Exposure of the natural product **3** to *tert*-BuOCl (**137**) in presence of $NEt_3$ at –78 °C induced ring closure and sigmatropic [1,5] rearrangement of the 2-*tert*-prenyl group affording flustramine C (**5**) in an isolated yield of 60% in six days. A mechanistic rationale was presented on the basis of $^{1}H,^{15}N$ HMBC experiments. It was confirmed that the treatment of **3** with *tert*-BuOCl (**137**) resulted in the chlorination of the aliphatic side chain amino group. Upon standing in $CDCl_3$ for one week, this halogenated intermediate **149** lost the side chain chloride ion and formed protonated flustramine C (**5**), presumably *via* transferring the side chain chlorine to form chloroindolenine **150** followed by ring closure to form **151** and [1,5] sigmatropic rearrangement of the 2-*tert*-prenyl group. Treatment of **152** with 2 M NaOH gave *rac*-flustramine C (**5**, Scheme 33).




Scheme 33: $^{1}H$ $^{15}N$ HMBC studies shed light on the formation of flustramine C (**5**).[116]

Although the formation of flustramine C (**5**) was efficient using *tert*-BuOCl, a remarkable improvement of this step was observed using NBS.[116] Deformylflustrabromine (**3**) dissolved in THF was reacted with 1 equivalent of NBS at 0 °C to afford *rac*-flustramine C (**5**) in an isolated yield of 71% within 2 h (Scheme 34).




deformylflustrabromine (**3**) *rac*-flustramine C (**5**)

Scheme 34: NBS-induced [1,5] prenyl shift to form flustramine C (**5**).[116,121]

## 3.3 Studies towards enantioselective synthesis of flustramine C

For the enantioselective synthesis of the natural product *rac*-flustramine C (**5**), it was necessary to reveal the optical rotation of the individual enantiomers. Until now, the optical activity for none of the individual enantiomers was reported.

### 3.3.1 Separation of (+)- and (–)-flustramine C

Deformylflustrabromine (**3**) and flustramine C (**5**) can be conveniently separated by reversed phase HPLC (Figure 14). When co-injected and eluted on a C-18 reversed-phase analytical column (LichroCART®, RP-18, particle size 5 µm, flow rate=0.9 mL/min) with MeOH/$H_2O$ (85:15), flustramine C (**5**) appeared at a retention time of 8.2 min whereas deformylflustrabromine (**3**) was eluted at 11.4 min.

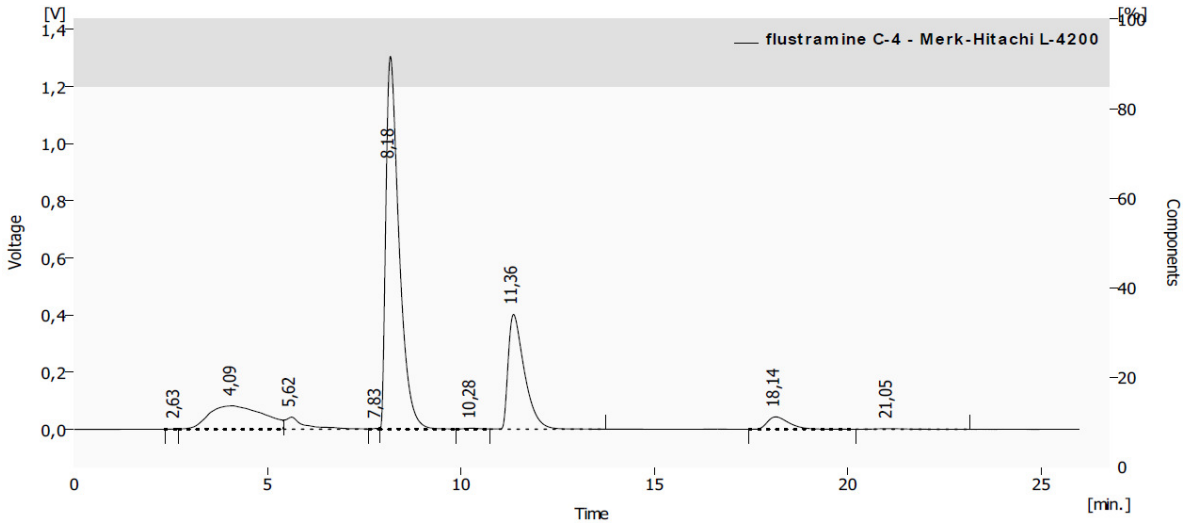



Figure 14: *Rac*-flustramine C (**5**) and deformylflustrabromine (**3**) were conveniently separated by reversed phase HPLC.

The individual enantiomers from synthetic *rac*-flustramine C (**5**) were conveniently separated on a chiral analytical column (Chiralcel OD, normal phase, particle size 10 µm).The solvent system was optimized to hexane–isopropanol in a ratio of 15:1 with a flow rate of 1.2 mL/min (Figure 15).

The enantiomer with the lower retention time (6.2 min) showed an optical rotational value of $[\alpha]_D^{21.6}$ = +153 ° (*c* = 0.79, $CHCl_3$) whereas the peak with delayed retention time (8.1 min) showed an optical rotation of $[\alpha]_D^{21.8}$ = –155 ° (c = 0.81, $CHCl_3$). Carlé and Christophersen did not report any optical activity for the isolated flustramine C (**5**).[24] However, Peters and co-workers re-isolated flustramine C (**5**) and determined the optical activity as $[\alpha]_D^{22}$ = –10.1 ° (c = 0.1, $CHCl_3$).[31] This implies that the isolated natural product flustramine C (**5**) is mostly racemic and the (–)-enantiomer with higher optical activity is responsible for the measured optical activity by Peters et al.

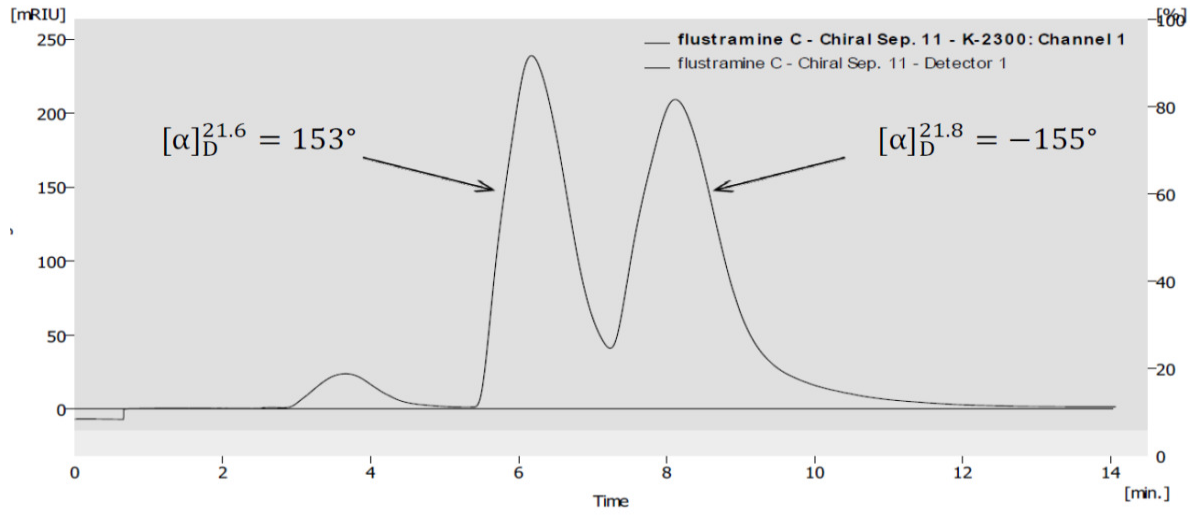
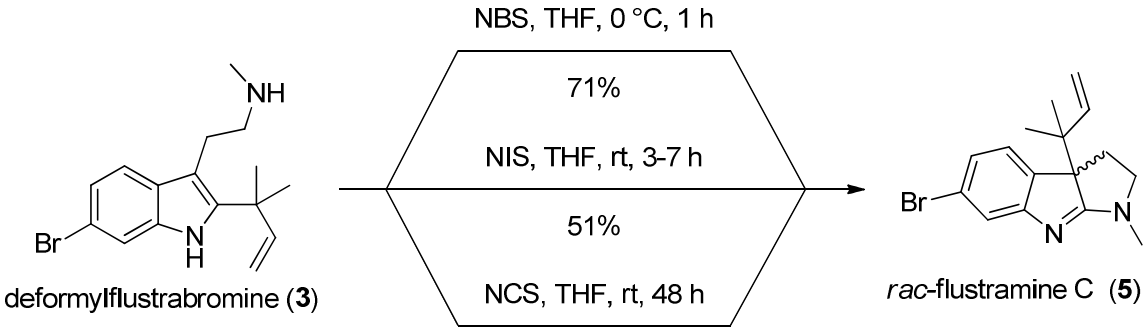



Figure 15: The individual enantiomers of *rac*-flustramine C (**5**) showed opposite values of optical rotation.

### 3.3.2 Use of hypervalent iodine reagents to form *ent*-flustramine C

Treatment of deformylflustrabromine (**3**) with NBS, NCS (*N*-chlorosuccinimide), and NIS (*N*-iodosuccinimide) resulted in *rac*-flustramine C (**5**) on every occasion. At the same time, there was a distinct difference in reaction times. With 1.0 equivalent of NBS, the reaction was complete in 1 h while 2.4 equivalents of NIS reacted slowly to complete the reaction in 3 hours. In the case of NCS, the reaction was even slower

and after 48 h of reaction time, there was plenty of unreacted starting material **3** (Scheme 35).

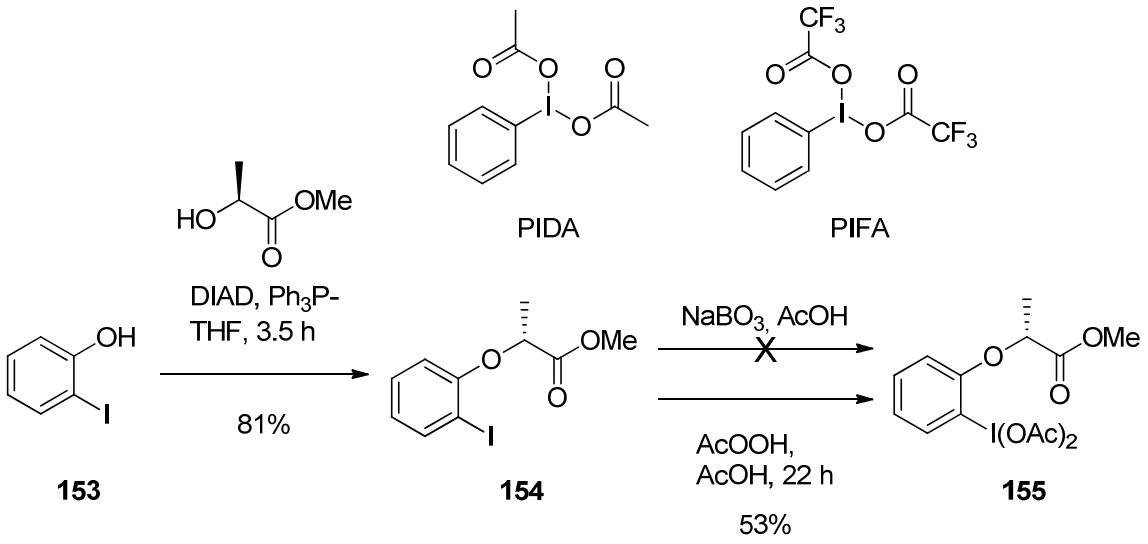



Scheme 35: *Rac*-flustramine C (**5**) was accessible by NBS, NIS, and NCS.

It was envisaged that the oxidative cyclization/rearrangement using a more electrophilic chiral halide reagent to form **5** was a direct way to get *ent*-flustramine C (**5**). As the reaction times were either faster with NBS or slower with NCS, NIS was chosen as potential parent compound of a enantioselective reagent. PIDA (Phenyliodo(III)diacetate) and PIFA (phenyliodo(III)*bis*(trifluoroacetate, shown in Scheme 36) were purchased from commercial suppliers, whereas the chiral reagent **155** was synthesized.

The synthesis of chiral reagent (*R*)-methyl-2-(2-(diacetoxyiodo)phenoxy)propanoate (**155**) commenced from 2-iodophenol (**153**).[117] Mitsunobu reaction of **153** with optically active methyl lactate inverted the stereogenic center of lactate to yield phenolether **154** in 81% yield. Oxidation of **154** with sodium perborate in acetic acid did not work. Alternatively, when **154** was reacted with *in situ* generated AcOOH in AcOH at 45 °C for 24 hours,[118] the desired chiral reagent **155** was isolated in 43% over two steps (Scheme 36).

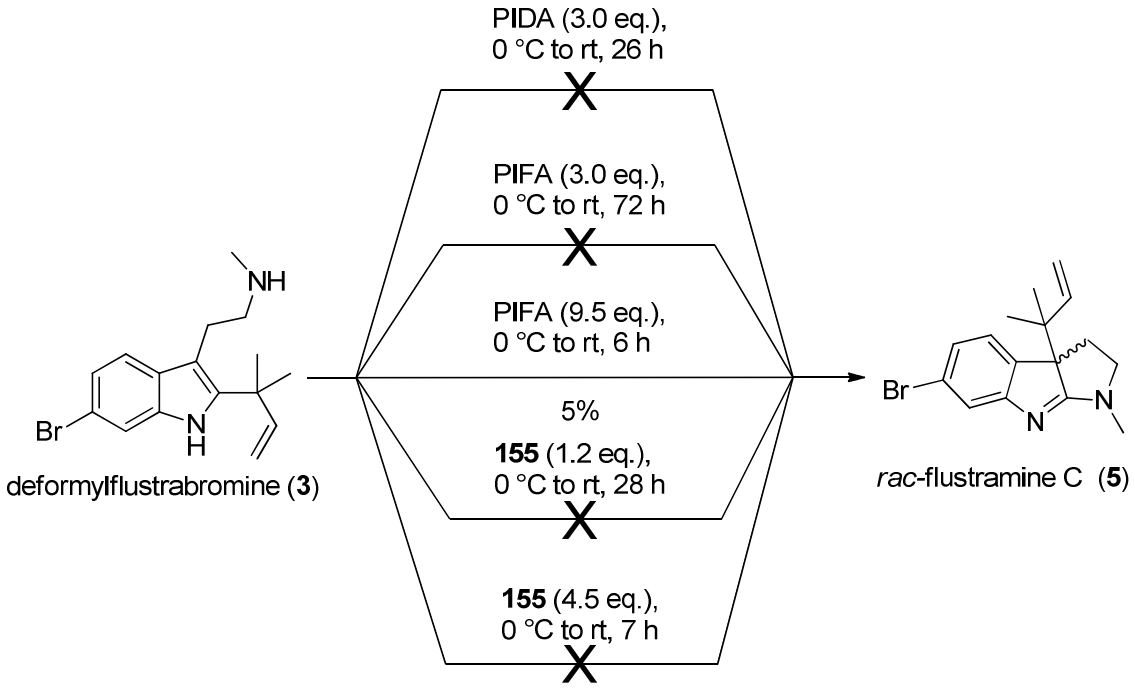
117. M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, *Tetrahedron Lett.* **2007**, *48*, 8691–8694.
118. A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2011**, *17*, 10538–10541.




Scheme 36: Hypervalent iodine reagents used as an alternative to NIS.

With the hypervalent iodine reagents in hand, deformylflustrabromine (**3**) was reacted with PIDA, PIFA, and chiral reagent **155**. In the first attempt, 3.0 equivalents of PIDA were reacted with **3**, but analysis by HPLC did not indicate any formation of flustramine C (**5**). Compound **5** was not detected either, when the reagent was changed to 3.0 equivalents of more electrophilic PIFA. However, increasing the amounts of PIFA to 9.0 equivalents formed *rac*-flustramine C (**5**) in low yield (5%). The majority of reagent PIFA remained in the reaction mixture and purification of **3** and **5** proved to be difficult. With the synthesized chiral reagent **155** (1.2 or 4.5 equivalents) no flustramine C (**5**) was formed (Scheme 37).

No further attempts were made on the synthesis of *rac*-flustramine C (**5**) using hypervalent iodine reagents. Apart from the evaluation of different hypervalent iodine reagents, fine tuning of solvent systems and additives might be alternative parameters to induce the formation of flustramine C (**5**).

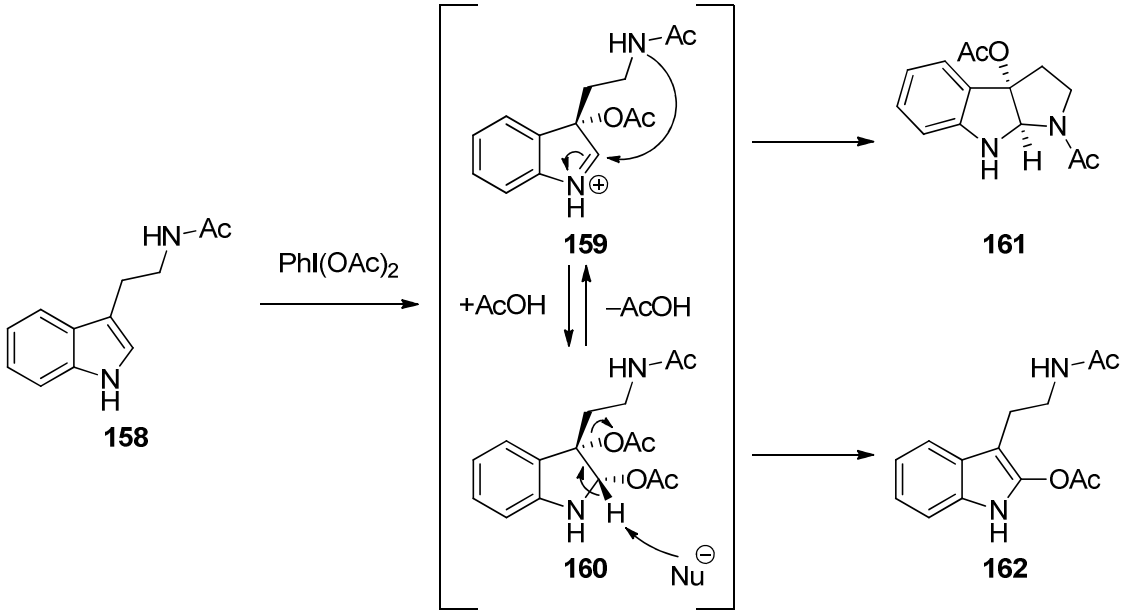



Scheme 37: Hypervalent iodine reagents were not helpful to form flustramine C (**5**).

Kajiyama and co-workers studied the oxidation of tryptamines using hypervalent iodine reagents.[119] Treatment of $N_b$-substituted tryptamines with PIDA resulted in formation of pyrrolo[2,3-*b*]indoles and 2-acetoxylated tryptamines with the highest yields of 38%. A mechanistic rationale for the formation of products of type **161** and **162** was described (Scheme 38). Moreover, the purification of the resulting products proved to be difficult due to fast degradation.

Recently, a variation of the method to synthesize functionalized pyrrolo[2,3-*b*]indoles was reported by Tu et al.[120] Tryptamines suitably protected at indole N-1 and at the aliphatic amine side-chain readily underwent intramolecular annulations to form pyrrolo[2,3-*b*]indoles (not shown in Scheme 38) by treatment with hypervalent reagents in presence of metalhalides in MeCN. Most of the transformations furnished the tricyclic products with yields up to 99%.

119. D. Kajiyama, T. Saitoh, S. Yamaguchi, S. Nishiyama, *Synthesis* **2012**, 1667–1671.
120. D. Tu, L. Ma, X. Tong, X. Deng, C. Xia, *Org. Lett.* **2012**, *14*, 4830–4833.

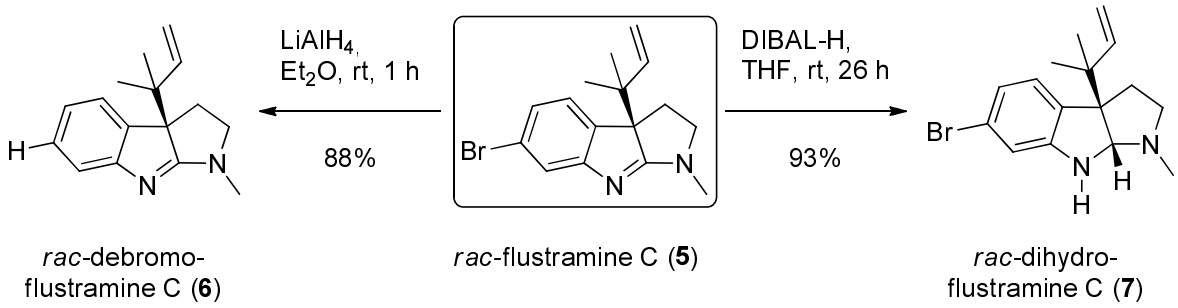



Scheme 38: Formation of pyrrolo[2,3-*b*]indoles (**161**) and acetoylindoles (**162**) in low yields (3-38%) by hypervalent iodine reagents.[119]

### 3.4 Synthesis of dihydroflustramine C

Another natural product isolated from *F. foliacea* is dihydroflustramine C (**7**). Reduction of the imine bond of **5** may furnish **7**.

The first attempt to effect this was made by Carlé and Christophersen. Flustramine C (**5**) reacted with 4.1 equivalents of $LiAlH_4$ to provide debromoflustramine C (**6**) in 88% yield (Scheme 39), but no reduction of the amidine moiety.[24]




Scheme 39: *Rac*-flustramine C (**5**) was reduced to *rac*-dihydroflustramine C (**7**).

The direct conversion of flustramine C (**5**) to *rac*-dihydroflustramine C (**7**) was achieved when **5** was treated with 1.8 equivalents of DIBAL-H at room temperature.

The imine bond of **5** was diastereoselectively reduced to form **7** in an isolated yield of 93% (Scheme 39) without debromination.

## 3.5 Scope of NBS-induced *tert*-prenyl rearrangements

NBS induced cyclization and rearrangement of a 2-*tert*-prenyl group to the indole 3-position occurred in a single pot transformation. The scope of this reaction was interesting. It was unclear whether the cyclization and rearrangement sequence reaction would work if:

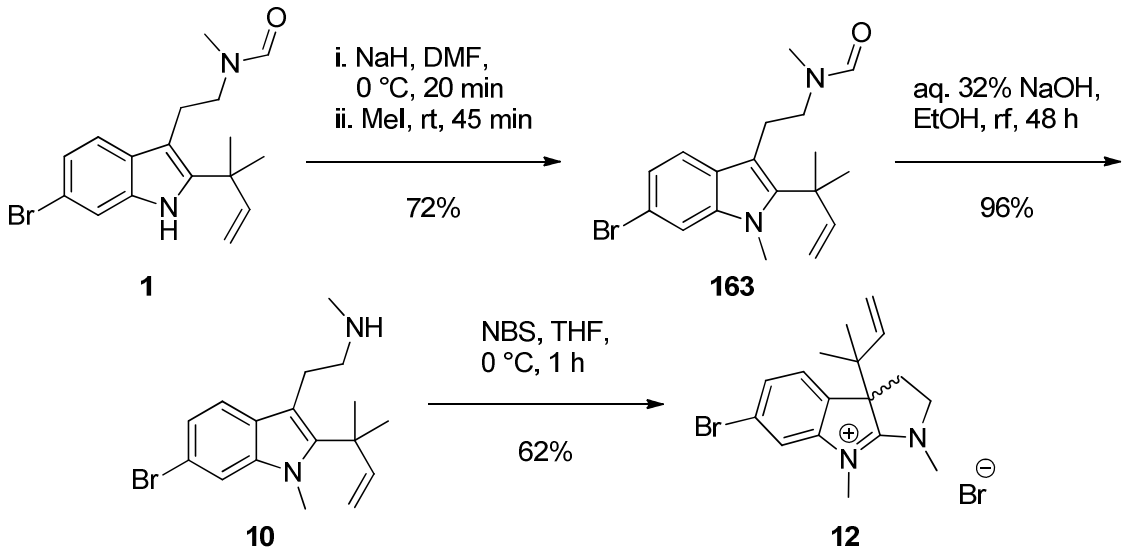
(a) the indole nitrogen in deformylflustrabromine (**3**) was protected with an alkyl group
(b) the bromine at the benzene section of the molecule was absent
(c) the starting material was methylated at N-1
(d) the methyl group at the aliphatic side chain was replaced by hydrogen
(e) the proton at the aliphatic secondary amine was replaced by a methyl group
(f) the aliphatic side chain carried a formyl group

To address all the above issues, a systematic study was carried out.[121]

### 3.5.1 Rearrangement of $N_a$-methyl-deformylflustrabromine (10)

Flustrabromine (**1**) was the optimal starting material to introduce the methyl group at the indole nitrogen. Following the standard conditions of treating indole **1** with NaH at 0 °C for 20 min and reaction with MeI provided the $N_a$-methyl-flustrabromine (**163**) in moderate yield of 72%. Deformylation was achieved upon refluxing **163** in aqueous ethanolic NaOH for 48 h to afford the key compound $N_a$-methyl-deformylflustrabromine (**10**) in 96%. Compound **10** was reacted with 1 equivalent of NBS which, as expected, induced the cyclization and 2,3-prenyl shift to form the *N*,*N*'-dimethylamidinium salt **12** (Scheme 40). The reaction was complete within 1 h and the product **12** precipitated as a colourless amorphous solid (62%).

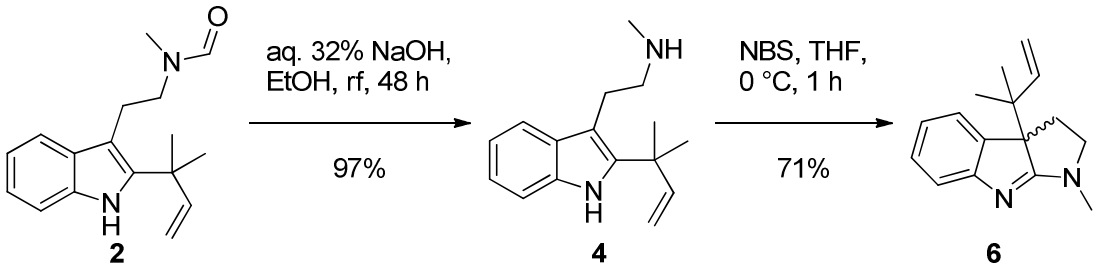
121. S. K. Adla, G. Golz, P. G. Jones, T. Lindel, *Synthesis* **2010**, *13*, 2161–2170.




Scheme 40: $N_a$-methyl-deformylflustrabromine (**10**) underwent cyclization and prenyl shift.

### 3.5.2 Rearrangement to form debromoflustramine C (6)

A starting material devoid of bromine on the benzene part of indole was desired for the preparation of debromoflustramine C (**6**). Debromoflustrabromine (**2**) was deformylated using the alkaline conditions as in the earlier cases to furnish debromodeformylflustrabromine (**4**) in 97%. NBS induced the cyclization and sigmatropic [1,5] shift of the 2-*tert*-prenyl group gave debromoflustramine C (**6**, 71% within 1 h, Scheme 41). Thus, the reaction was equally good even in the absence of the bromine substituent. No side products were isolated, as in the other examples. This synthetic route provided debromoflustramine C (**6**), for the first time, with an overall yield of 36% in 6 steps.

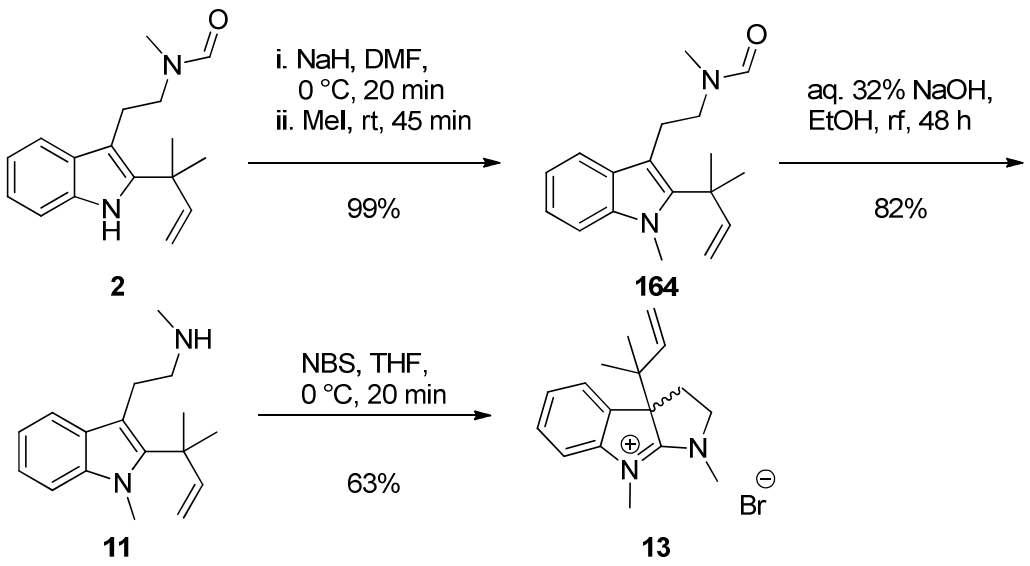



Scheme 41: 2-*Tert*-prenyl shift occurred on debromodeformylflustrabromine (**4**).

### 3.5.3 Rearrangement of debromo-$N_a$-methyl-deformylflustrabromine (11)

The scope of the sigmatropic [1,5] prenyl shift reaction was thus evaluated with two parameters changed. The bromine was absent on the benzene section of the precursor and the indole NH was protected by a methyl group. Methylation of the indole nitrogen was achieved in excellent yield of 99% to result in **164**. Compound **164** was deformylated and reacted with 1 equivalent of NBS. Stretching the scope of oxidative cyclization and rearrangement by NBS, compound **164** was oxidized to result in *N*,*N*'-dimethylamidinium salt **13** (63%, Scheme 42).

The precipitate formed in the flask was washed with EtOAc to result in clean **13**. The amidinium salt **13** showed a characteristic imine resonance at δ = 180.9 ppm in the $^{13}$C NMR spectrum. X-ray crystallography of **13** confirmed the presence of bromide as counter ion (Figure 16).




Scheme 42: Formation of *N*,*N*'-dimethylamidinium salt **13** *via* cyclization and rearrangement.

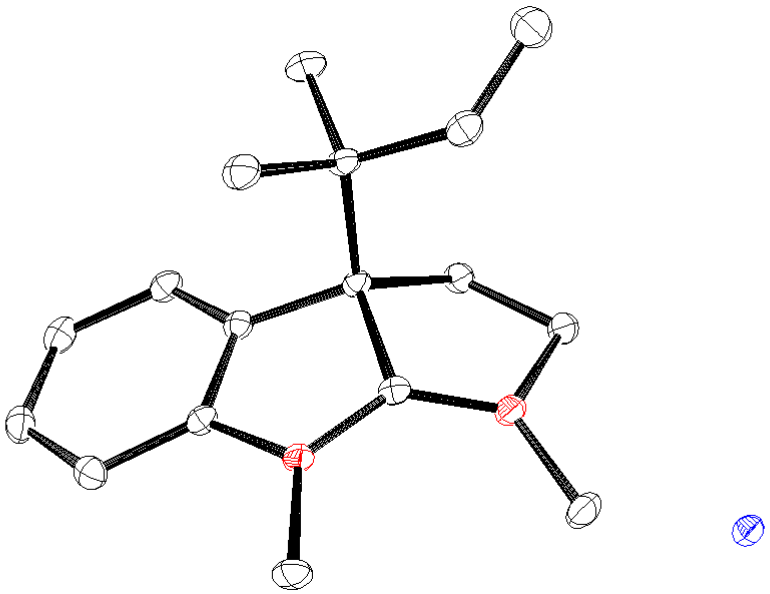


Figure 16: ORTEP drawing of *N*,*N*'-dimethylamidinium salt **164**; hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

### 3.5.4 Rearrangement on 2-*tert*-prenyltryptamine (16)

Oxidative rearrangement of 2-*tert*-prenyl-methyltryptamine analogues **4**, **10**, and **12** also worked well. From these experiments it was concluded that neither the presence of bromine nor the presence of an indole proton was necessary. Now, 2-*tert*-prenyltryptamine (**16**) was prepared with an absent side-chain methyl group.

Tryptamine (**124**) was reacted, in presence of $Et_3N$, with phthalic anhydride in boiling toluene for 8 hours. The precipitate formed was recrystallized from MeOH to obtain the pure compound **165** (86%) as fine needles for which an X-ray crystal structure was established (Figure 17). There exist slight variations in phthalimide protection methodologies.[122,123,124]

122. Q. Zeng, Z. Liu, B. Li, F. Wang, *Amino Acids* **2004**, *27*, 183–186.
123. B. S. Jursic, P. K. Patel, *Carbohydr. Res.* **2006**, *341*, 2858–2866.
124. Y. Liu, S. Luo, X. Fu, Fang, Z. Zhuang, W. Xiong, X. Jia, H. Zhai, *Org. Lett.* **2006**, *8*, 115–118.

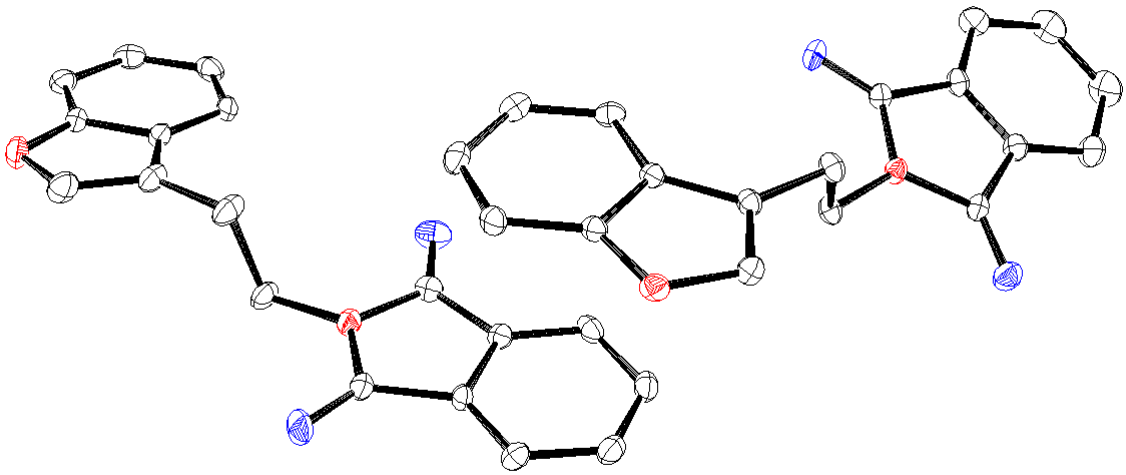
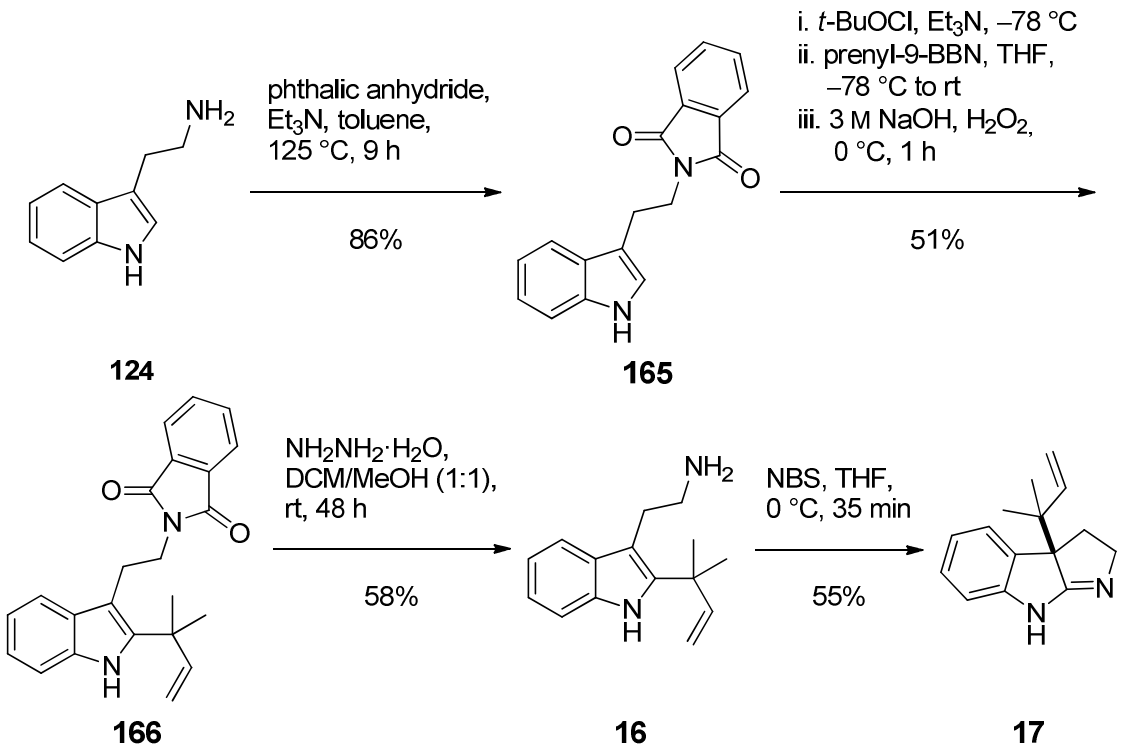


Figure 17; ORTEP drawings of phthalimide protected tryptamine **165**; hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

Phthalimide protected tryptamine **165** was subjected to Danishefsky's *tert*-prenylation at the indole 2-position. Reaction of **165** with *tert*-BuOCl at –78 °C in THF generated the transient chloroindolenine which was treated with prenyl-9-BBN (**142**). Addition of 3 M NaOH and $H_2O_2$ to the reaction mixture afforded the 2-*tert*-prenylated indole **166**. Recrystallisation from $CHCl_3$/hexane (1:5) afforded the product **166** (51%). After successful introduction of the *tert*-prenyl group, the compound **166** was subjected to hydrazinolysis. The compound **166** was dissolved in a mixture of MeOH/DCM (1:1) and reacted with 2.8 equivalents of hydrazine monohydrate at ambient temperature for 48 h to provide **16**. The free amine **16** was reacted with NBS at 0 °C for 35 min. NBS-induced cyclization/2-*tert*-prenyl shift occurred, albeit in a lower yield (55%, Scheme 43).

This experiment confirmed that the aliphatic side-chain methyl group was not necessary for the ring closure and 2-*tert*-prenyl rearrangement sequence.

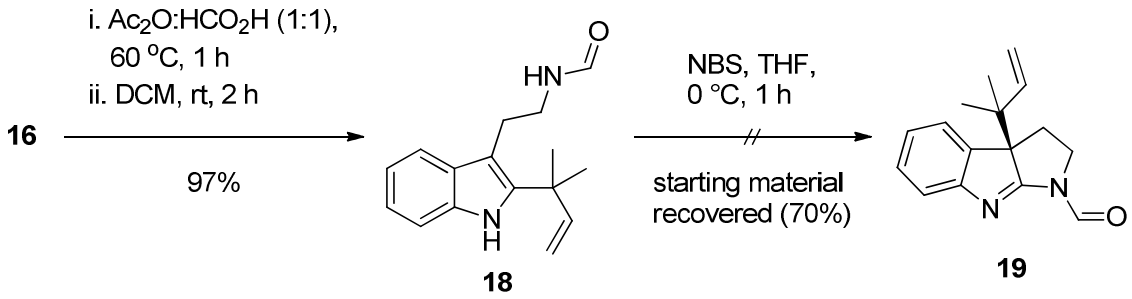
Regular prenylation at N-8 position of the tricycle **17** followed by introduction of a methyl substituent, as shown by Kawasaki et al. for the synthesis of *rac*-flustramine C (**5**),[44] may furnish *rac*-debromoflustramine A.




Scheme 43: Cyclization/rearrangement of 2-*tert*-prenyltryptamine (**16**).

### 3.5.5 Rearrangement of 2-*tert*-prenylformamide 18

When the free amine **16** was treated with a mixture of $Ac_2O/HCO_2H$ for 2 h, 2-*tert*-prenylated formyltryptamine **18** was formed in an excellent yield of 97%. However, reaction of the formamide **18** with NBS did not induce oxidative rearrangement to afford pyrrolo[2,3-*b*]indole **19**. The starting material was recovered in good quantity (70%, Scheme 44).




Scheme 44: 2-*Tert*-prenylformyltryptamine (**18**) was reluctant to undergo oxidation.

It was confirmed that the aliphatic side-chain should not bear an amide group to undergo oxidation/rearrangement to form formylated pyrrolo[2,3-*b*]indoles.

### 3.5.6 Rearrangement of $N_b$,$N_b$-dimethyl-2-*tert*-prenyltryptamine (20)

The synthesis commenced at debromoflustrabromine (**2**). Reduction of the formyl group of **2** with 4.2 equivalents of DIBAL-H proceeded smoothly to result in dimethylated compound **20**. No chromatography was needed (86%). Compound **20** was dissolved in acetone for solubility reasons and reacted with NBS. Surprisingly, after the work-up with 2 M NaOH, 3-bromo-2-*tert*-prenylindole (**22**) was obtained as a minor product (21%) and as the least polar component from the reaction. Analysis of the NMR spectrum of the major product showed that all signals of the product **23** had very similar chemical shifts as the starting material apart from the aliphatic side-chain signals shifted to up-field region. Elemental analysis and X-ray crystallography (Figure 18) confirmed this major product as the hydrobromide salt of the starting material **20** (58%, Scheme 45).

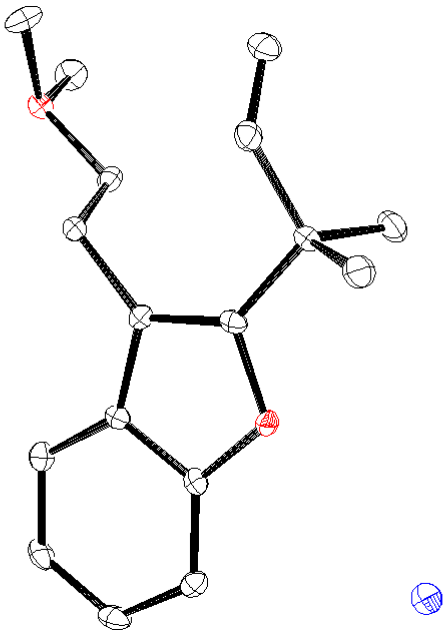
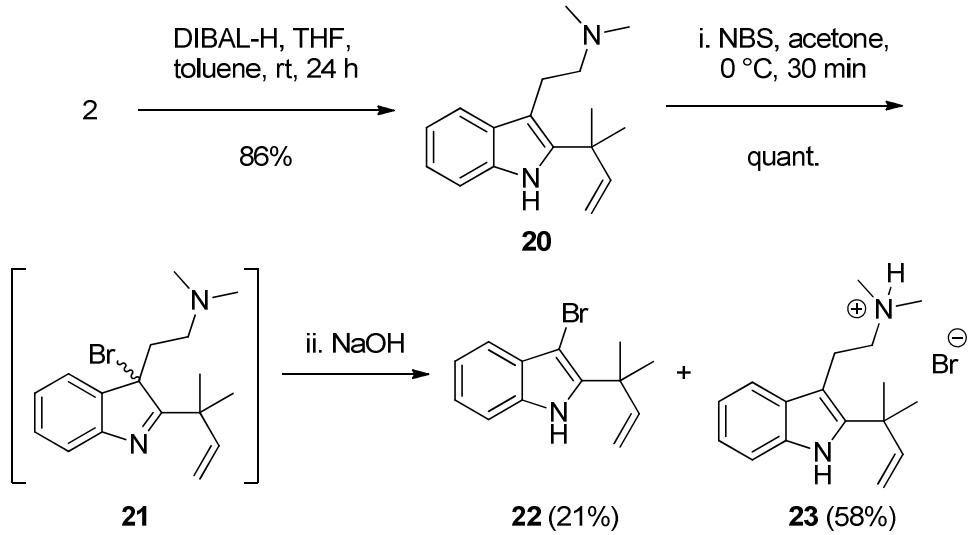
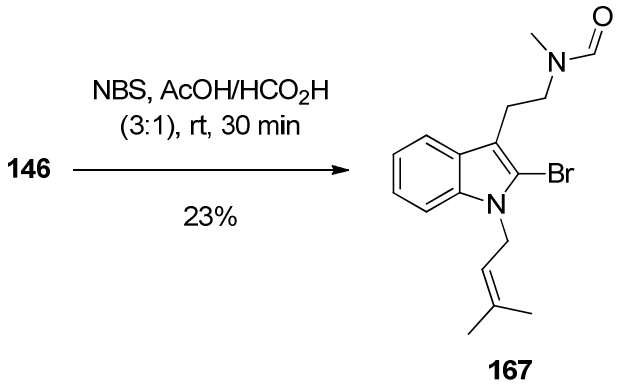


Figure 18: ORTEP drawing of HBr salt of $N_b$,$N_b$-dimethyl-2-*tert*-prenyltryptamine (**20**); hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

Neither prenyl rearrangement nor bromination at the benzene part occurred when N-prenylated 2-unsubstituted indole **146** was treated with NBS in an acidic mixture of AcOH and $HCO_2H$ (3:1). Unstable, yet isolable, 2-brominated prenylindole **167** was isolated as black oil which degraded readily at room temperature (23%, Scheme 46).




Scheme 45: Unexpected outcome of the treatment of **20** with NBS.




Scheme 46: 2-Unsubstituted N-prenylindole **146** preferred bromination at C-2 over prenyl shift.

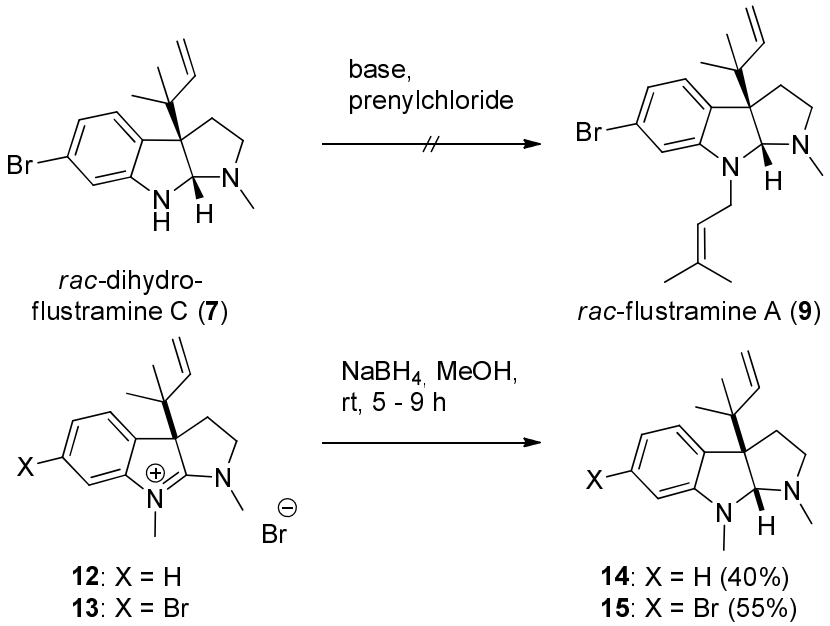
### 3.6 Synthesis of *rac*-flustramine A

*Rac*-dihydroflustramine C (**7**) was synthesized from flustrabromine (**1**) in 3 steps (65%). Prenylation at N-8 of **7** would afford the natural product *rac*-flustramine A (**9**).

In the earlier experiments, reaction of **7** with either NaH or $K_2CO_3$ followed by prenylbromide did not result in *rac*-flustramine A (**9**). Analysis by GC-MS (EI) indicated that compound **7** had degraded and resulted only in peaks below *m/z* 220 compared to 320/388 for dihydroflustramine C (**7**)/flustramine A (**9**).

Treatment of **7** with DIBAL-H for four days did not lead to reduction of the amidinium salt. Meanwhile, reduction of the *N*,*N*'-dimethylamidinium salts with $NaBH_4$ had been

published.[57] Indeed, replacement of DIBAL-H with $NaBH_4$ afforded the product (**14**) with the newly introduced hydrogen placed at C-8a of **14** albeit in moderate yield (40%). The reduction procedure was also performed on the structurally similar compound **13**, affording the reduced product **15** (55%, Scheme 47).




Scheme 47: $NaBH_4$ reduced the *N*,*N*'-dimethylamidinium salts effectively.

For compound **14**, in the $^1H$ NMR spectrum, a sharp singlet at δ = 4.20 ppm (Figure 19) and in the $^{13}C$ NMR spectrum a signal at δ = 91.4 ppm (Figure 20) confirmed the introduction of the new proton at the bridgehead 8a position.

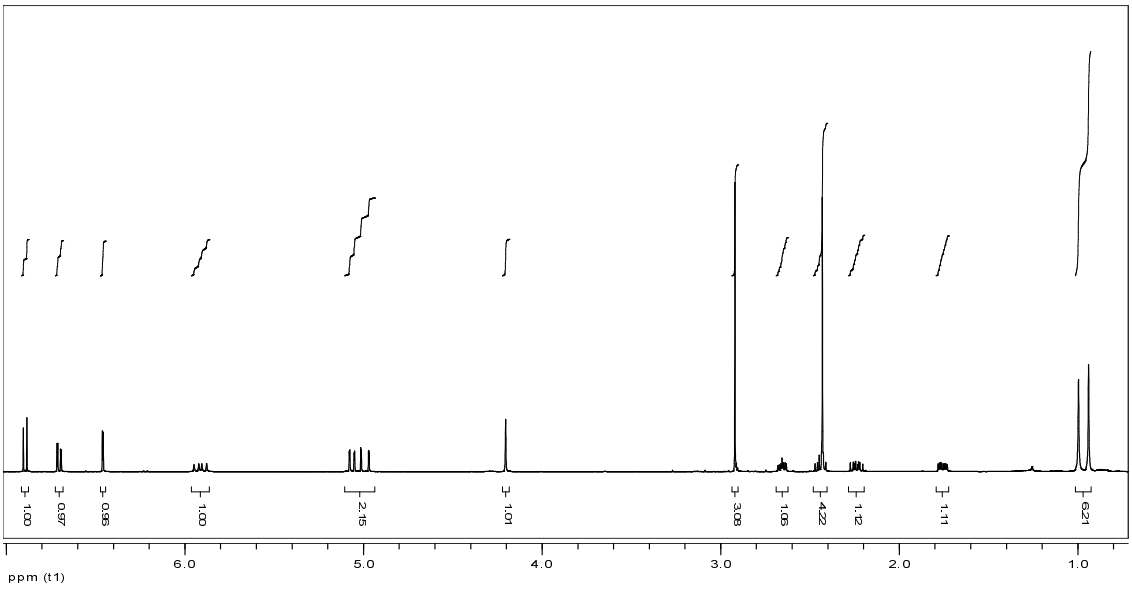



Figure 19: $^1H$ NMR spectrum (400 MHz, $CDCl_3$) of compound **14**.

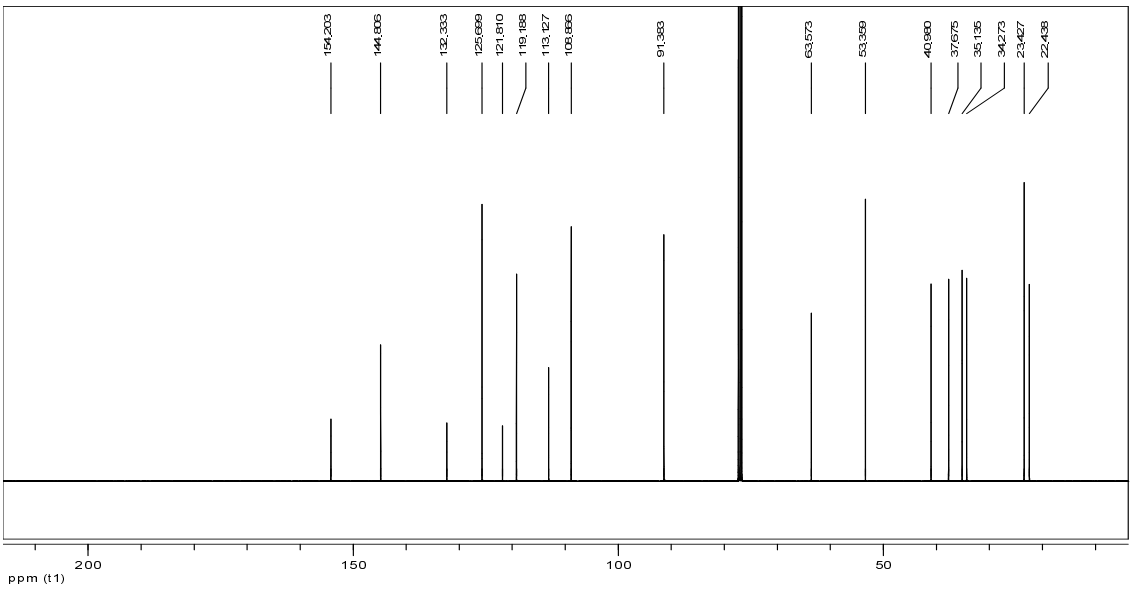



Figure 20: $^{13}C$ NMR spectrum (100 MHz, $CDCl_3$) of compound **14**.

Encouraged by this result, an alternative strategy for proton replacement at N-1 in flustrabromine (**1**) with a prenyl group, followed by oxidation with NBS to the amidinium salt and successive reduction to *rac*-flustramine A (**9**) was envisaged. However, new questions arose: (a) how to introduce the prenyl group regioselectively? (b) would the oxidative rearrangement reaction work on a doubly prenylated precursor? (c) if the cyclization and prenyl shift work, what will be the priority of prenyl migration?

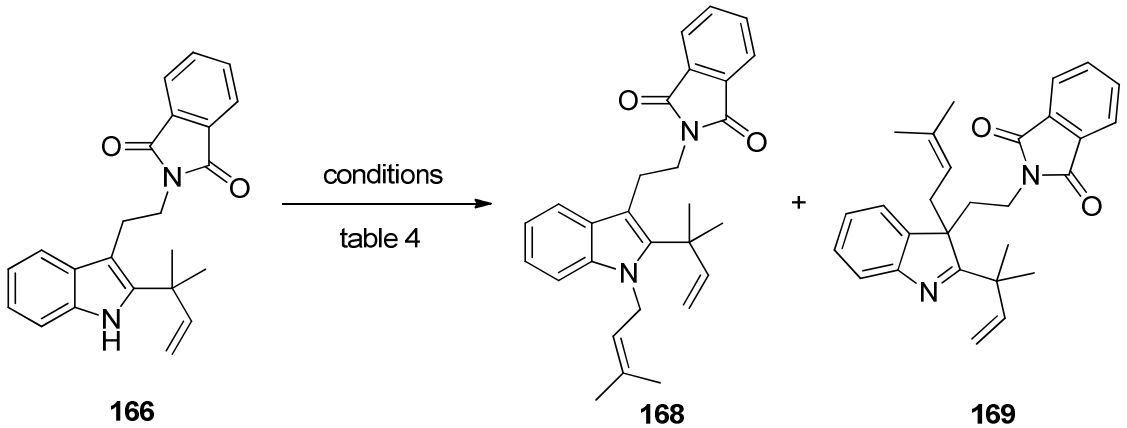
### 3.6.1 Unexpected prenylation on 2-*tert*-prenylated phthalimide 166

Indole prenylation is an important step in natural product synthesis and biosynthesis. The biosynthesis of prenylated tryptophan alkaloids was investigated by Williams et al.[125,126] whereas Li published the chemoenzymatic synthesis of prenylated indole alkaloids of fungal origin.[127] Recently, Lindel et al. reviewed the strategies and technologies available for prenylation towards the total synthesis of indole alkaloids.

125. R. M. Williams, E. M. Stocking, J. F. Sanz-Cervera, *Top. Curr. Chem.* **2000**, *209*, 97–173.
126. Y. Ding, J. R. de Wet, J. Cavalcoli, S. Li, T. J. Greshock, K. A. Miller, J. M. Finefield, J. D. Sunderhaus, T. McAfoos, S. Tsukamoto, R. M. Williams, D. H. Sherman, *J. Am. Chem. Soc.* **2010**, *132*, 12733–12740.
127. S.-M. Li, *Nat. Prod. Rep.* **2010**, *27*, 57–78.

With a few exceptions for *tert*-prenylation at indole 4-, 5-, and 6-positions, it is possible either to *tert*-prenylate or regularly prenylate all positions of indole.[128]

Prenylation was attempted of the phthalimide protected *tert*-prenylindole **166** to preserve valuable amounts of natural product **1**. A solution of **166** in DMF was added to NaH at –20 °C followed by 1.5 equivalents of prenylbromide. After two days of reaction, there were substantial amounts of unreacted starting material (61%) along with the desired product **168** in low yield (22%). The reaction temperature was increased from –20 °C to 0 °C and loading of base/prenyl source was changed from 1.5/1.5 to 1.8/1.8 equivalents. However, a marginal increase in the yield (29%) of the desired product **168** along with the recovery of starting material (45%) was observed. Finally, increasing the amounts of NaH to 5.0 equivalents and prenylchloride to 4.0 equivalents showed an unexpected prenylation pattern. In a ratio of 1:4, the desired N-prenylated indole **168** was formed in the lowest yield of 16% whereas the C-3 prenylated regioisomer **169** resulted as the major product with 62% yield (Table 4). Further attempts towards selective C-3 prenylation or N-prenylation of **166** were not undertaken.



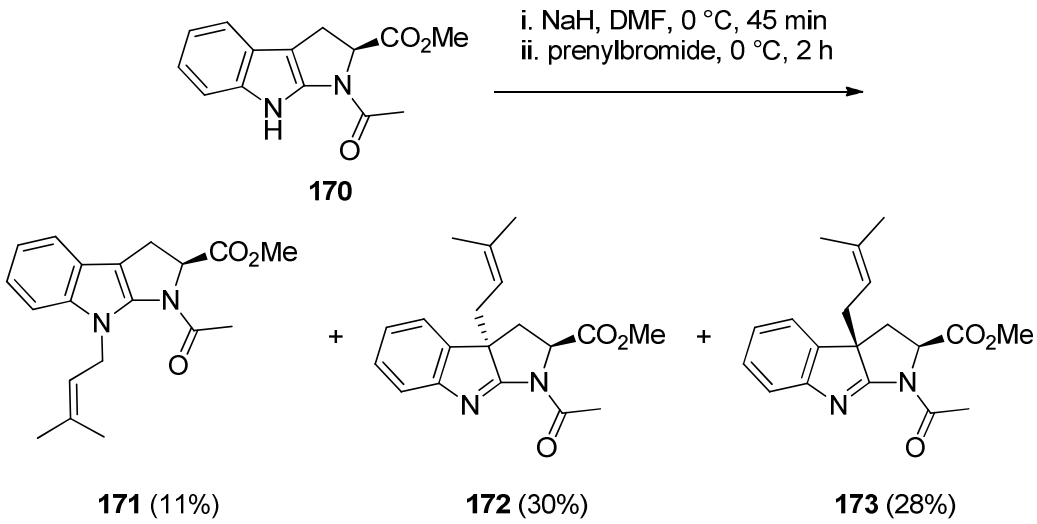

**166** **168** **169**

Table 4: Prenylation on **166** gave unexpected non-regioselectivity.

| Base/prenyl-X (eq.) | Conditions | 168 | 169 | SM recovered |
|---|---|---|---|---|
| 1.5/1.5 | i. NaH, DMF, –20 °C, 90 min<br>ii. prenylbromide, –20 °C, 12 h, then rt, 2 d | 22% | - | 61% |
| 1.8/1.8 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, 0 °C, 2 d, then rt, 4 d | 29% | - | 45% |
| 5.0/4.0 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 6 h | 16% | 62% | - |

128. T. Lindel, N. Marsch, S. K. Adla, *Top. Curr. Chem.* **2012**, *309*, 67–129.

Towards the first total synthesis of (–)-debromoflustramine B (**51**), Cardoso and co-workers encountered a similar situation. On reaction with NaH and prenylbromide in DMF at 0 °C compound **170** underwent predominant C-3 prenylation (58%) compared to formation of the N-prenylindole (11%, Scheme 48).[56,57]

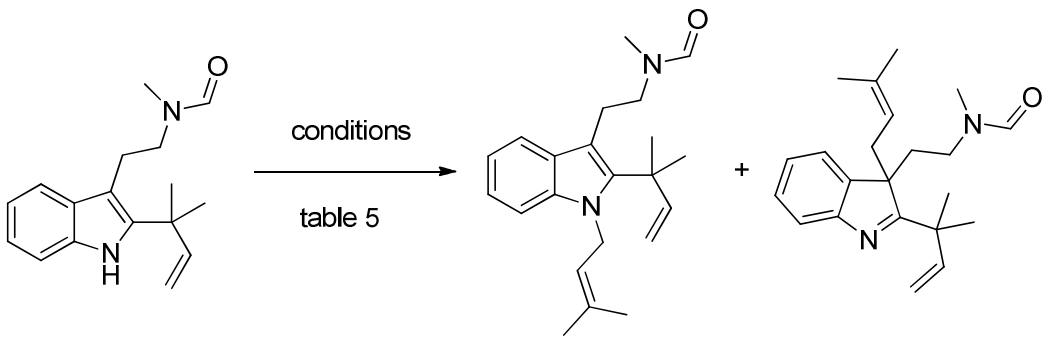



Scheme 48: Predominant C-3 prenylation as reported by Cardoso et al.[56,57]

### 3.6.2 Non-regioselective prenylation on 2 and flustrabromine (1)

Reaction of debromoflustrabromine (**2**) with 1.8 equivalents of NaH and then 1.8 equivalents of prenylchloride at 0 °C for 24 h resulted in the desired N-prenylated indole **27** (33%). As in the case of **166**, unreacted starting material **2** was recovered (22%). However, by increasing the equivalents of base and prenylchloride to 5.0 and 4.0, respectively, a combined yield of 89% was achieved of doubly prenylated regioisomers **27** (37%) and **174** (52%, Table 5).

Using silica gel column chromatography with EtOAc-petrolether as solvent system, separation of doubly prenylated indoles **27** and **174** was accomplished.




**2** **27** **174**

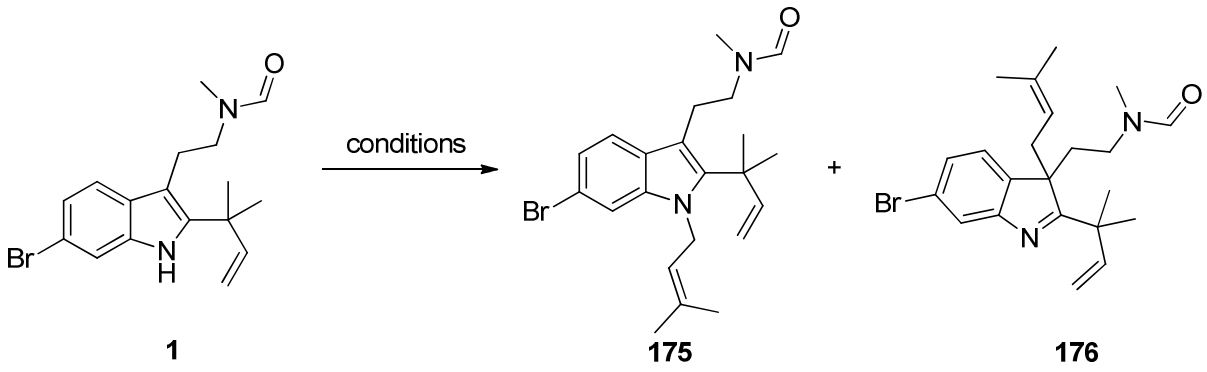
Table 5: Optimization of prenylation on debromoflustrabromine (**2**).

| Base/prenyl-X (eq.) | Conditions | 27 | 174 | SM recovered |
|---|---|---|---|---|
| 1.8/1.8 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 1 d | 33% | | 22 |
| 5.0/4.0 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 6 h | 37% | 52% | - |

Upon reaction of **1** with 1.5 equivalents of both NaH and prenylbromide at –20 °C for 2 days, flustrabromine (**1**) failed to react. Even by altering the reaction temperature from –20 °C to 0 °C and the prenyl source from prenylbromide to prenylchloride, no prenylation of flustrabromine (**1**) took place. However, performing the reaction at room temperature for two days furnished the desired N-prenyl-flustrabromine (**175**) as a minor product (10-14%). The major product isolated was C-3-prenylated flustrabromine (**176**) in a yield of 60%.

By increasing the amounts of NaH and prenylchloride to 1.8 equivalents, a balanced formation of each regioisomer was observed (28% for **175** and **176**). In the last attempt, 5.0 equivalents of NaH and 4.0 equivalents of prenylchloride were used to generate the desired N-prenylated indole **175** in the highest isolated yield of 41% while the C-3 prenylated regioisomer **176** was the major product with a yield of 50%. Table 6 highlights the optimization results regarding prenylation of flustrabromine (**1**).

Purification of doubly prenylated products **175** and **176** by normal phase silica gel column chromatography proved difficult as both regioisomers exhibited very close retention factors in different solvent systems. However, reversed phase (C-18) column chromatography with MeOH/$H_2O$ (5:1) resulted in a facile separation of regioisomers **175** and **176**.

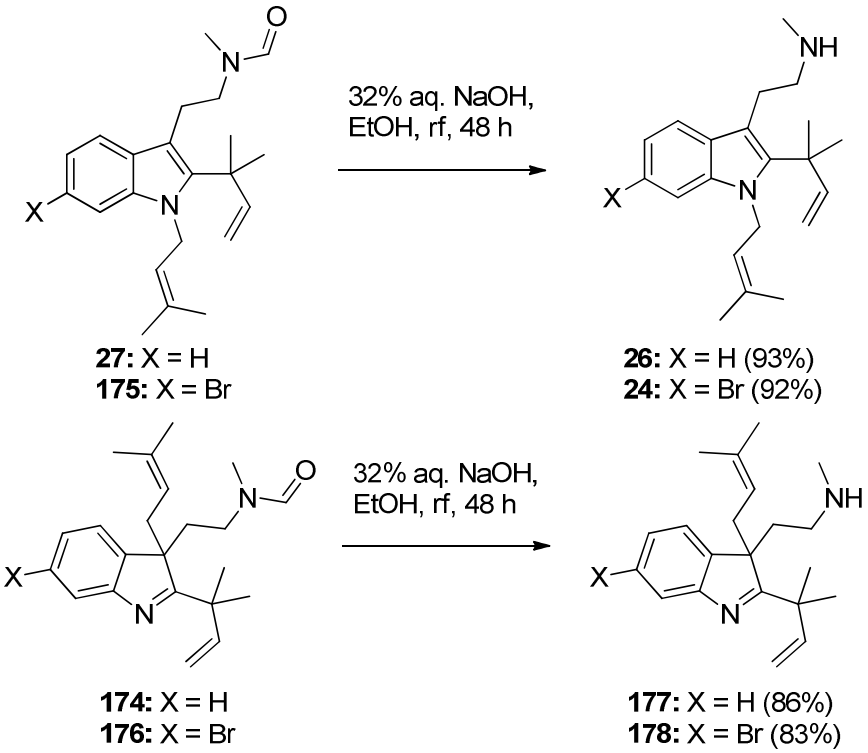



**1** **175** **176**

Table 6: Prenylation on **1** gave N-1 and C-3 prenylated regioisomers **175** and **176**.

| Base/prenyl-X (eq.) | Conditions | 175 | 176 | Comment |
|---|---|---|---|---|
| 1.5/1.5 | i. NaH, DMF, –20 °C, 90 min<br>ii. prenylbromide, –20 °C, 2 d | - | - | No reaction |
| 1.5/1.5 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, 0 °C, 2 d | - | - | No reaction |
| 1.5/1.5 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 2 d | 10-14% | 40% | - |
| 1.8/1.8 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 2 d | 28% | 28% | - |
| 5.0/4.0 | i. NaH, DMF, 0 °C, 2 h<br>ii. prenylchloride, rt, 1 d | 41% | 50% | - |

The doubly prenylated indoles were smoothly deformylated in excellent yields. In a general procedure, prenylated indoles were refluxed in 32% aqueous NaOH in ethanol for 48 h resulting in $N_a$-prenylated and C-3 prenylated secondary amines with yields above 83%. The products were obtained in high purity without further purification (Scheme 49).



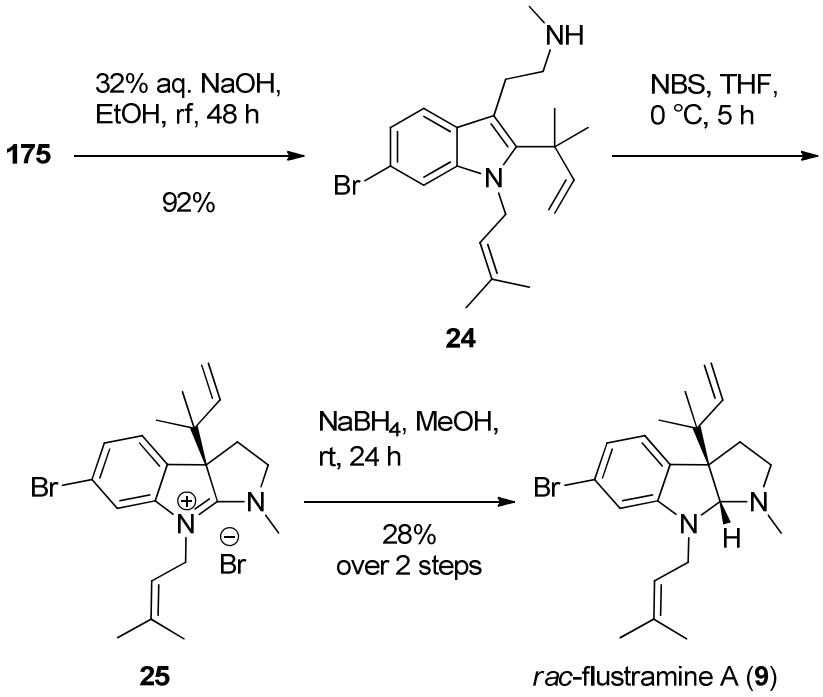

Scheme 49: Deformylation resulted in secondary amines in high yields.

### 3.6.3 Completion of the synthesis of *rac*-flustramine A

$N_a$-prenyl-flustrabromine (**175**) was dissolved in EtOH and refluxed in 32% aqueous NaOH for two days to afford $N_a$-prenyl-deformylflustrabromine (**24**) in an excellent yield of 92%. The doubly prenylated indole **24** was reacted with NBS at 0 °C. Once again, NBS-induced oxidative ring closure and sigmatropic [1,5] prenyl group rearrangement took place to form amidinium salt **25**.

Unlike other NBS-induced oxidations, the reaction of **24** with NBS was slow and took 5 h for completion. The salt **25** was soluble in organic solvents such as $CHCl_3$, DCM, and MeOH and purification of **25** by reversed phase HPLC using MeOH/$H_2O$ (80:20) as mobile phase resulted in the isolation of pure **25** (26%) with loss of substantial amounts of product. When **25** was reacted with 0.8 equivalents of $NaBH_4$ at room temperature for 24 h *rac*-flustramine A (**9**) was obtained in 54% yield.

$N_a$-prenyl-deformylflustrabromine (**24**) in THF was treated with NBS to result in *N*-prenyl-*N*'-methyl amidinium salt **25**. The crude concentrate was dissolved in MeOH and was treated under inert atmosphere with $NaBH_4$. Purification by reversed phase HPLC resulted in *rac*-flustramine A (**9**) in 28% over two steps (Scheme 50).




Scheme 50: Lindel's oxidative 2-*tert*-prenyl shift resulted in *rac*-flustramine A (**9**).

A *tert*-prenyl group, a regular prenyl group, indole protons, and diastereotopic protons had remained intact. The new proton at C-8a appeared as a sharp singlet at δ = 4.36 ppm in the $^{1}$H NMR spectrum (Figure 21) whereas δ = 89.4 ppm was observed for the C-8a in the $^{13}$C NMR spectrum (Figure 22). All other analytical data were in good agreement with those published in the literature.

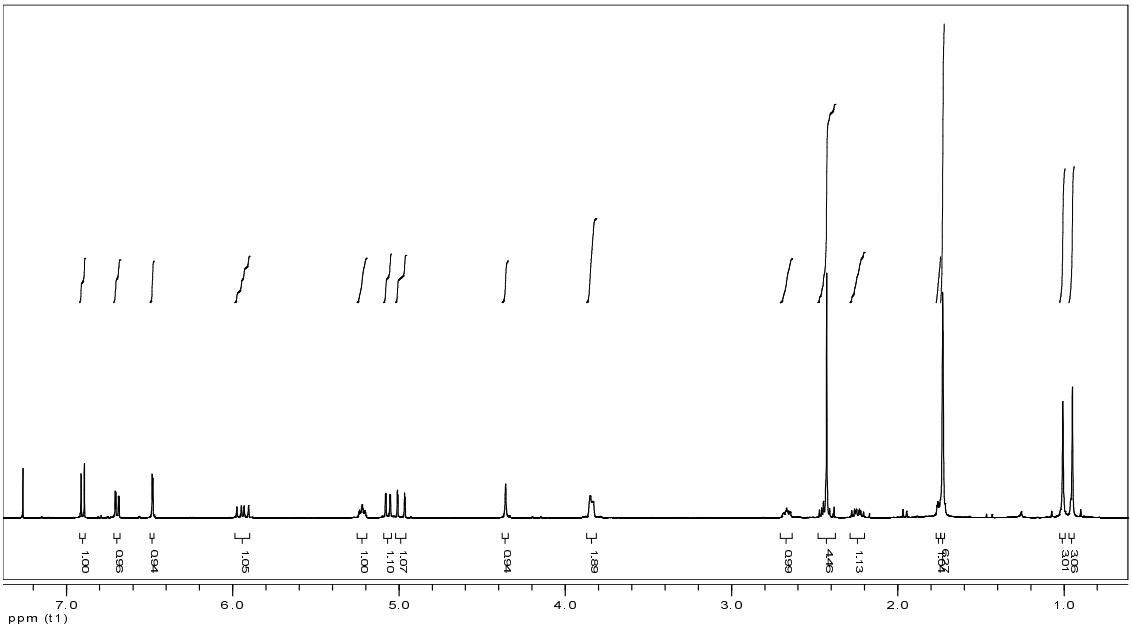



Figure 21: $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-flustramine A (**9**).

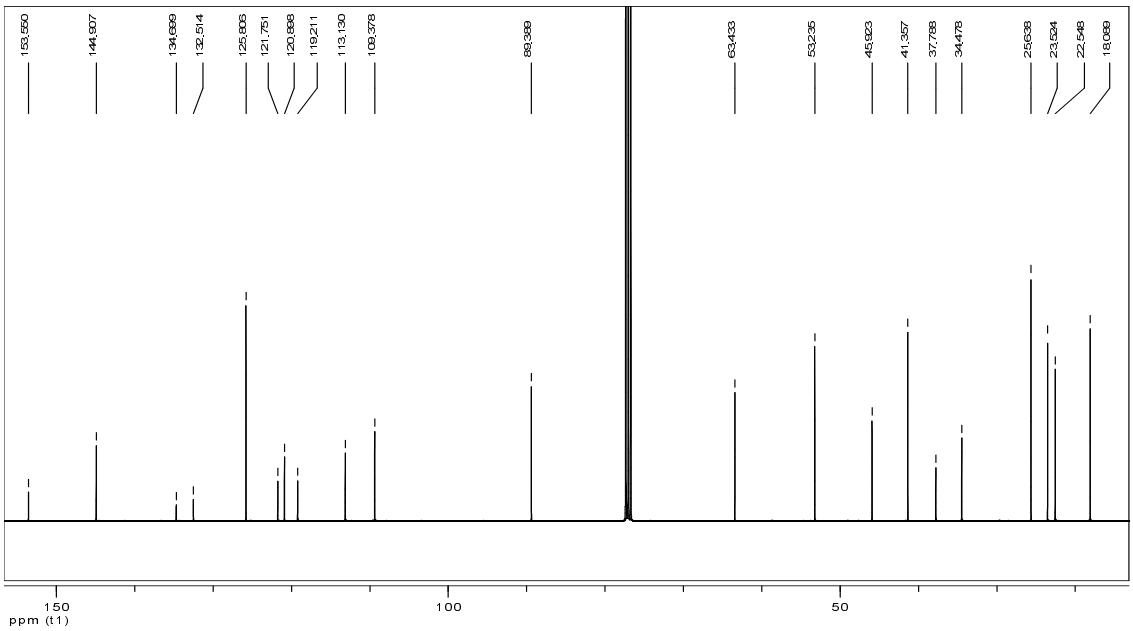



Figure 22: $^{13}C$ NMR spectrum (100 MHz, $CDCl_3$) of *rac*-flustramine A (**9**).

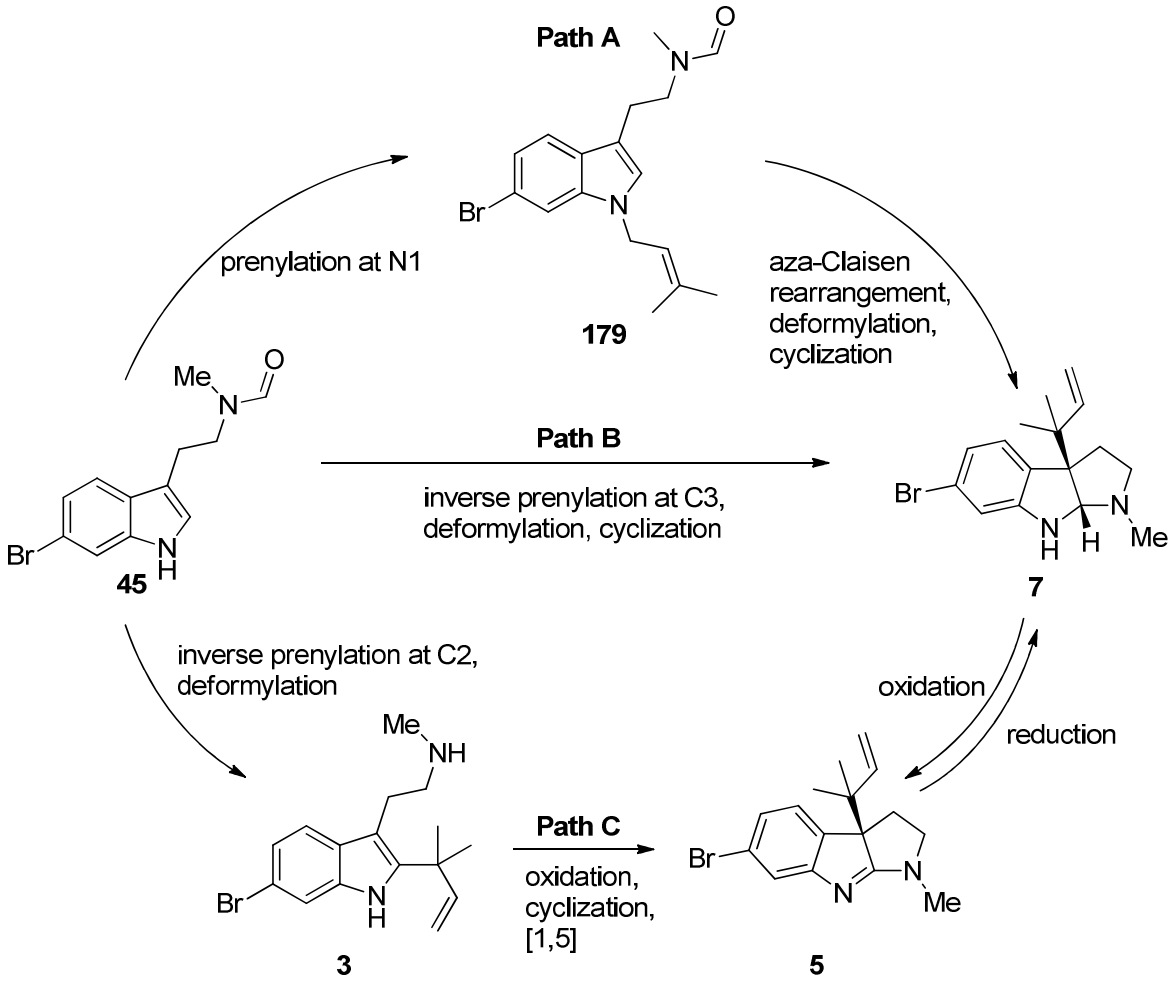
Debromo-$N_a$-prenyl-flustrabromine (**27**) was deformylated by boiling in ethanolic 32% aqueous NaOH to furnish the doubly prenylated precursor **26**. It might be possible to cyclize and rearrange the compound **26** to *rac*-debromoflustramine A.

### 3.6.4 Possible biosynthesis of flustramine C, dihydroflustramine C, and flustramine A

The biomimetic synthesis of flustramine C (**5**) and dihydroflustramine C (**7**) was addressed by Lindel et al (Scheme 51).[116] The biosynthesis of the natural product dihydroflustramine C (**7**) could proceed via three major pathways. Starting at natural product **45**, regioselective N-prenylation could result in **179**. Aza-Claisen rearrangement of the prenyl group from N-1 to the 3-position of the indole and deformylation of the C-3 *tert*-prenylindole followed by cyclization would furnish the natural product **7** (path A, Scheme 51). Alternatively, starting at the same natural product **45**, inverse prenylation by $S_N2'$ reaction at C-3 and deformylation followed by ring closure would result in dihydroflustramine C (**7**, path B, Scheme 51). A similar strategy was proposed by Bhat and co-workers for the biosynthesis of roquefortine.[85,86]

In contrast to pathways A and B, a direct 2-*tert*-prenylation could occur resulting in the known *Flustra* alkaloid flustrabromine (**1**). Deformylation of **1** would result in

*Flustra* secondary metabolite deformylflustrabromine (**3**). Successful oxidative cyclization followed by 2-*tert*-prenyl migration would furnish the pyrrolo[2,3-*b*]indole **5**. The rearrangement may proceed in any of the two s of the molecule. Any enantiocontrol of the rearrangement step would result in exclusive enantiomers with defined optical rotations. Diastereoselective reduction of the imine **7** may lead to dihydroflustramine C (**7**, path C, Scheme 51). The proposed pathway C was proven by chemical synthesis of dihydroflustramine C (**7**).[116,121]

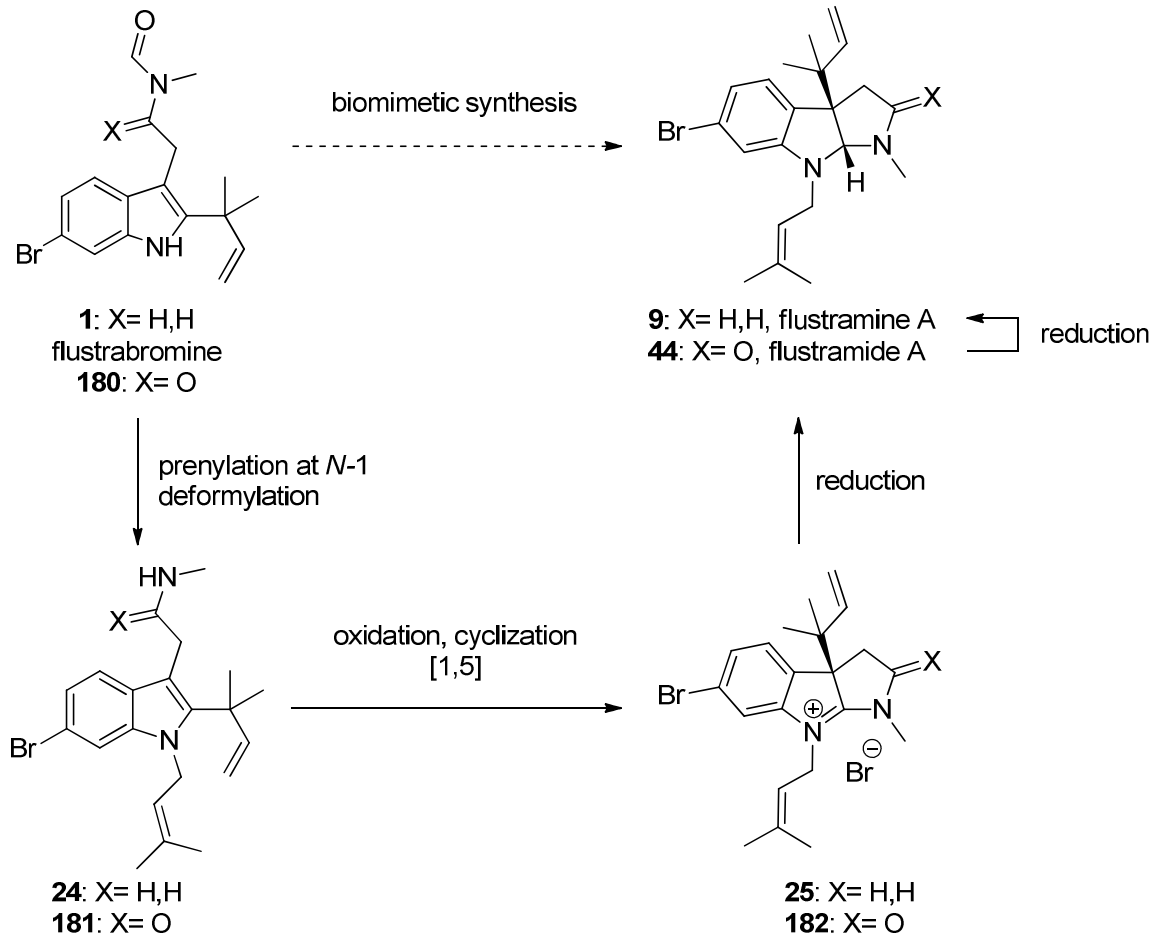



Scheme 51: Possible biosynthesis of dihydroflustramine C (**7**) *via* deformylflustrabromine (**3**).[116]

Addressing the biosynthesis of roquefortine, Barrow et al.[87] and Gorst-Allmann et al.[88] proposed that the aza-Claisen rearrangement of a N-prenyl group results in the C-2 *tert*-prenyl intermediate which subsequently undergoes sigmatropic [1,5] rearrangement to furnish the C-3 *tert*-prenylindoles. Recently, Li et al. and Williams et al. showed the biochemical transformation of 2-*tert*-prenylated precursor

notoamide E (**121**) into 3-*tert*-prenylated notoamide C (**122**) using the prenyl transferase NotB.[91] A similar pathway of 2-*tert*-prenyl migration was proposed by Stocking et al. regarding the biosynthesis of paraherquamide A.[129]

Further support to the proposal by Lindel et al. regarding the biomimetic synthesis of flustramines was demonstrated by the successful construction of *rac*-flustramine A (**9**). Wulff et al. isolated the natural products flustrabromine (**1**) and flustramide A (**44**). Considering the fact that both **1** and **44** were isolated from the same extract of *Flustra foliacea*, it is possible that flustrabromine (**1**) is a biomimetic precursor for flustramide A (**44**) which in turn may be converted to flustramine A (**9**, Scheme 52).




Scheme 52: Biomimetic *rac*-flustramine A (**9**) synthesis from flustrabromine (**1**).

Starting at the natural product flustrabromine (**1**) and **180**, selective N-prenylation and deformylation would result in the formation of $N_a$-prenyl-deformylflustrabromine

129. (a) E. M. Stocking, J. F. Sanz-Cervera, R. M. Williams, *Angew. Chem. Int. Ed.* **1999**, *38*, 786–789. (b) E. M. Stocking, R. M. Williams, J. F. Sanz-Cervera, *J. Am. Chem. Soc.* **2000**, *122*, 9089–9098.

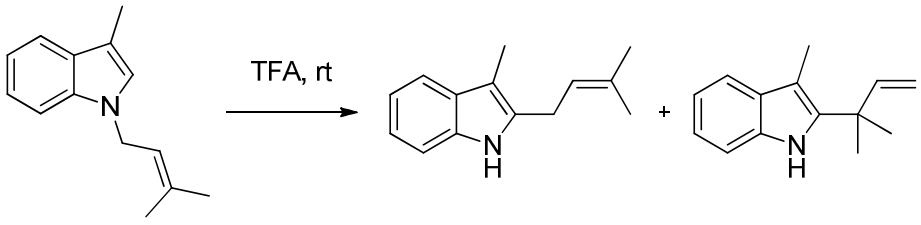
(**24**) and **181**. Upon oxidative ring closure and 2-*tert*-prenyl shift compounds **24** and **181** would furnish the amidinium salts **25** and **182**. Upon reduction at the 8a-position salt **182** would furnish the natural product flustramide A (**44**). Morales-Ríos et al.,[37] Kawasaki et al.[41,42], and Trost et al.[43] had shown the successful conversion of flustramide A (**44**) to flustramine A (**9**). Therefore, flustramide A (**44**) could be the biomimetic precursor to flustramine A (**9**).

It could be also possible that $N_a$-prenyl-deformylflustrabromine (**24**) is a natural product yet to be isolated.

### 3.7 Behavior of prenylindoles under acidic and non-oxidative conditions

Regular prenyl groups are often sensitive to acids and high temperatures. Apart from the NBS-induced oxidative *tert*-prenyl rearrangements, attempts to shift the prenyl groups under acidic and microwave conditions were made.

The rearrangement of N-prenylindoles to 2-prenylindoles is well studied. In early publications, Casnati et al. studied echinulin-type compounds and reported the conversion of an N-prenylated compound to a mixture of C-2 *tert*-prenylated and C-2 regularly prenylated compounds. When 3-methyl-*N*-prenylindole (**183**) was refluxed in TFA for 1 hour, unequal amounts (70:30) of **184** and **185** were formed. However, when the reaction was carried out at 0 °C for 7 days, a shift in the amounts (35:65) of **184** and **185** was observed (Scheme 53).[130,131]



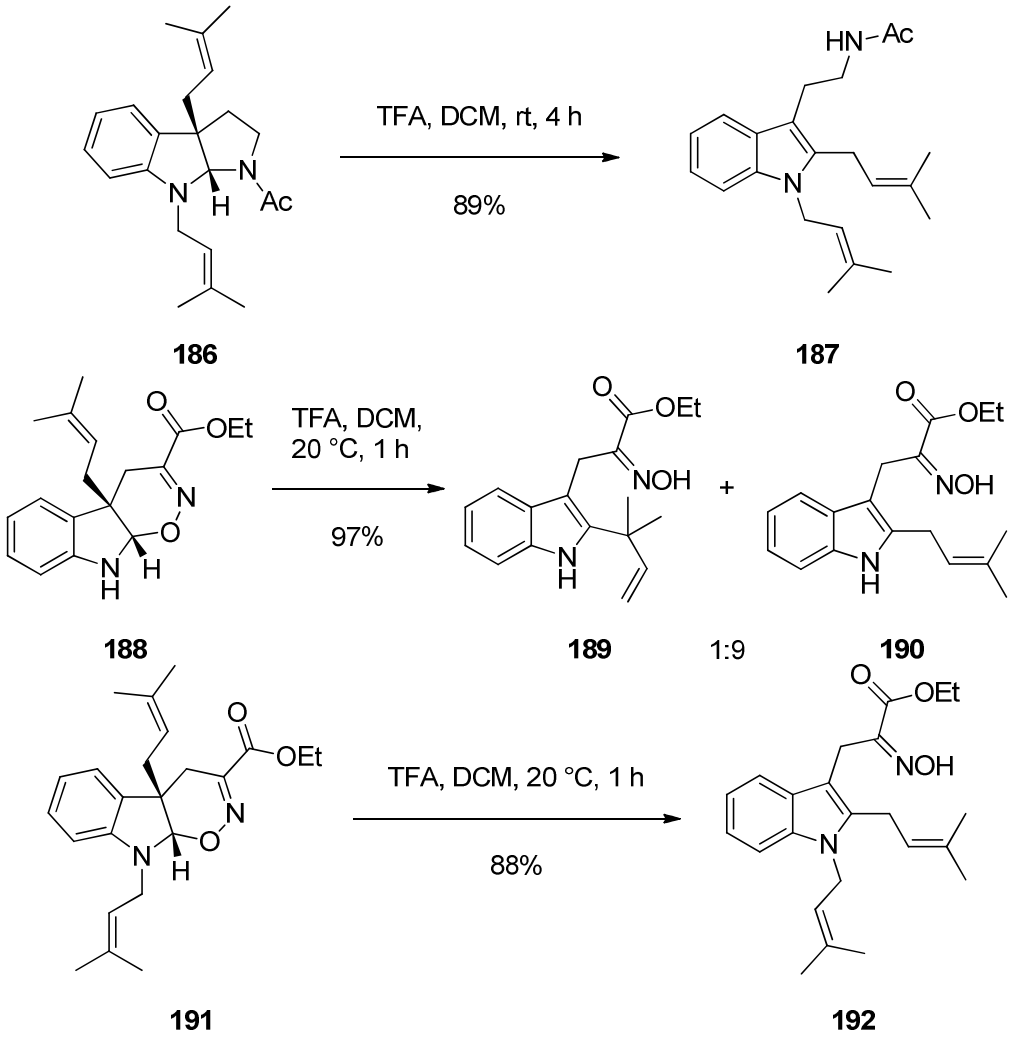

**183** **184** **185**

Scheme 53: TFA induced N-prenyl migration on 2-unsubstituted indoles.[130,131]

Nakagawa showed that 3a-prenylated pyrrolo[2,3-*b*]indole **186** reacted with TFA in DCM, as a shift of the 3a-prenyl group occurred to form 2-prenylindole **187** with

130. G. Casnati, A. Pochini, *J. Chem. Soc.* **1970**, 1328–1329.
131. G. Casnati, A. Pochini, *J. Chem. Soc. Perkin Trans. 1* **1974**, 754–757.

simultaneous opening of the pyrrolidine ring (89%).[132] In a similar attempt, Plate et al. published the reaction of 3a-prenylindole **188** with 5.0 equivalents of TFA in DCM at room temperature, which furnished the 2-prenylindole **190** and C-2 *tert*-prenylindole **189** in a 9:1 ratio within 1 h. It was found that when two regular prenyl groups at N-1 and C-3a are available, the N-prenyl group did not undergo rearrangement. Only the C-3a prenyl group was shifted to the indole 2-position (Scheme 54).[133]

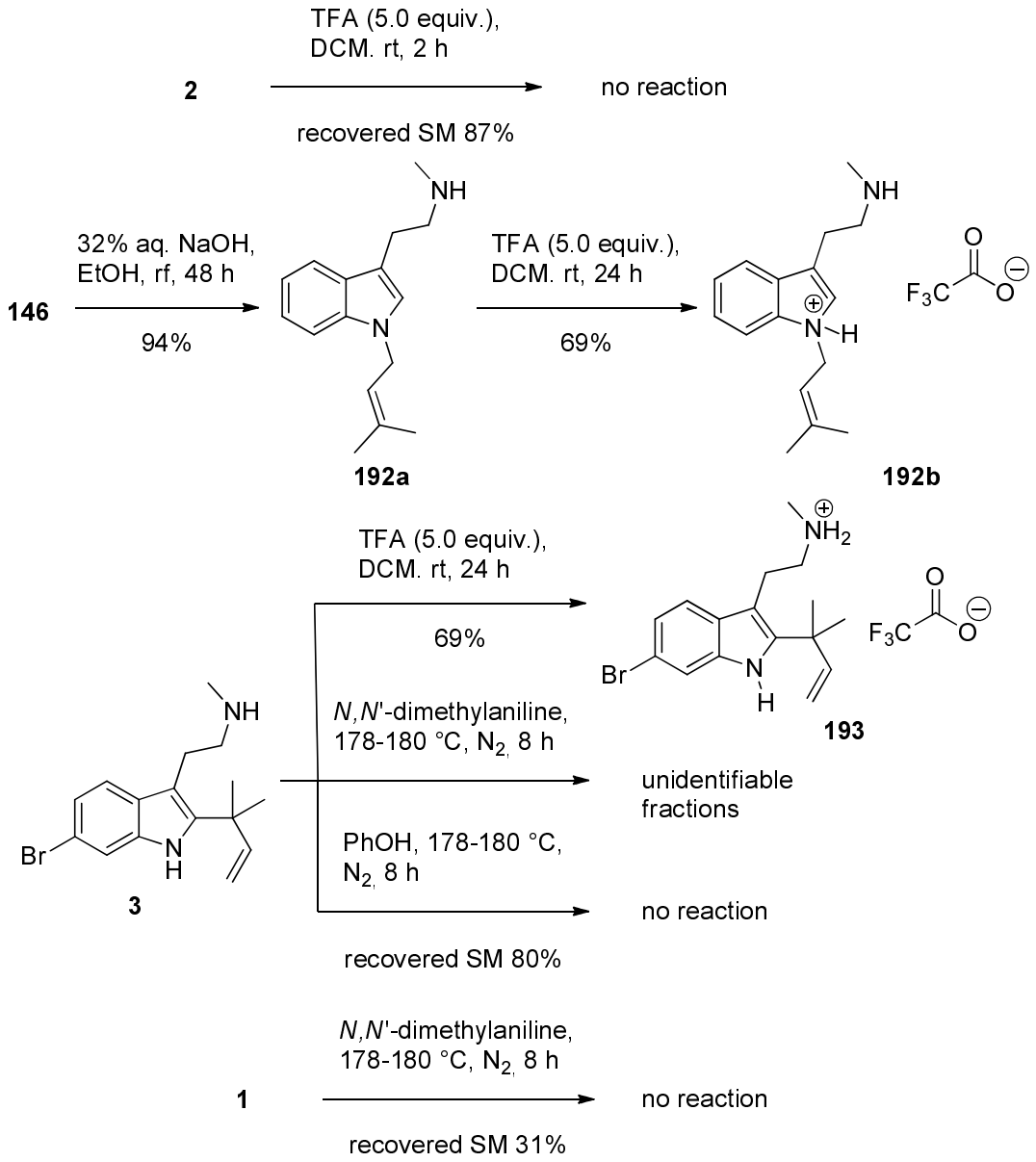



Scheme 54: TFA-mediated rearrangements of regular prenylindoles.[132,133]

Acid-mediated reactions of 2-*tert*-prenylindoles were interesting. In one experiment, debromoflustrabromine (**2**) was allowed to react with 5.0 equivalents of TFA. Unfortunately, no reaction had taken place after 2 h and 87% of the starting material

132. M. Nakagawa, K. Matsuki, T. Hino, *Tetrahedron Lett.* **1983**, *24,* 2171–2174.
133. R. Plate, H. C. J. Ottenheijm, *Tetrahedron Lett.* **1986**, *27*, 3755–3758.

was recovered. In same conditions, **192a** gave **192b**. However, when deformylflustrabromine (**3**) was exposed to 5.0 equivalents of TFA in DCM for 24 hours, the TFA salt **193** was formed (Scheme 55). Due to disorder in the olefinic bond of the *tert*-prenyl group, the X-ray crystal structure of **193** is not presented.

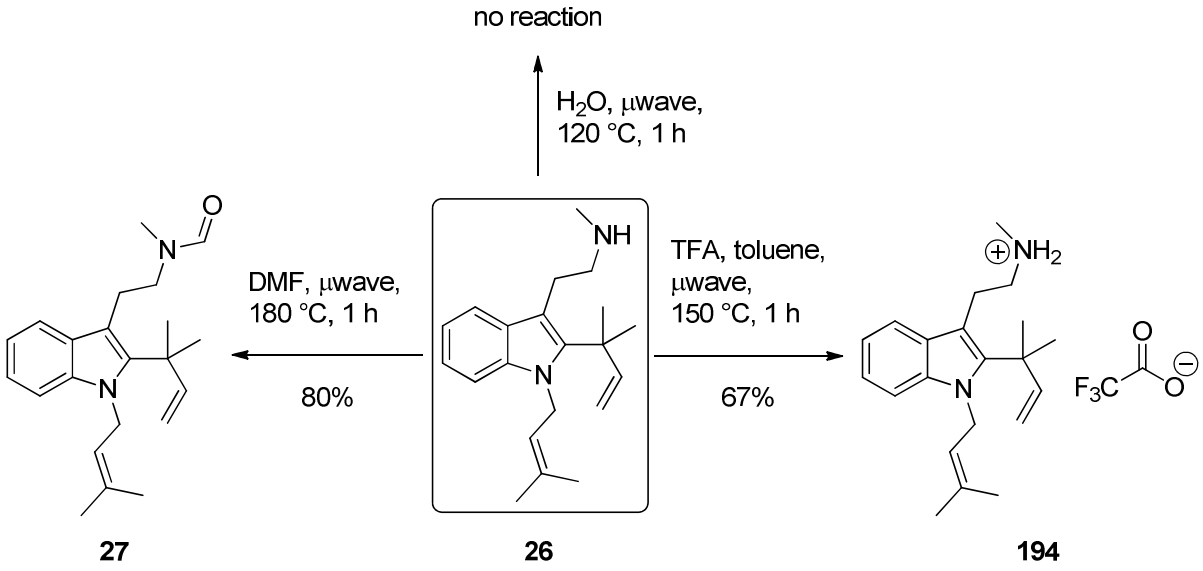



Scheme 55: 2-*tert*-prenylindoles were stable to TFA and higher temperatures

Next, flustrabromine (**1**) and deformylflustrabromine (**3**) were heated to 180 °C for 8 h in *N*,*N*-dimethylaniline. The solvent was UV-absorbent at 254 nm and overshadowed the TLC control and thus purification of the reaction mixture was not possible. Only in the case of flustrabromine (**1**), the starting material was recrystallized (31%). *N*,*N*-Dimethylaniline was replaced with PhOH as another high

boiling solvent and deformylflustrabromine (**3**) was refluxed again at 180 °C for 8 hours. Unfortunately, no thermal rearrangement of the 2-*tert*-prenyl group took place and starting material was recovered (80%, Scheme 55).

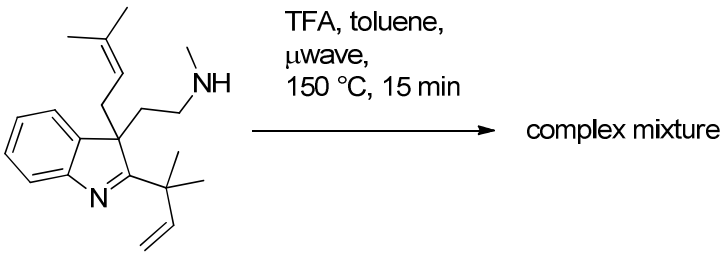
Furthermore, the thermal stability was evaluated by heating the doubly prenylated secondary amine **26** which was obtained from the deformylation of **27**. In an early experiment, compound **26** in $H_2O$, although not soluble, was packed in a sealed tube and irradiated under microwave conditions at 120 °C for 1 h with a power of 500 W. No reaction took place and starting material was recovered (82%). The temperature and the solvent were changed in the next experiment. Compound **26** was dissolved in toluene and 0.5 equivalents of TFA and irradiated at 150 °C for 1 h to afford the TFA salt **194** (67%). When **26** in DMF was irradiated at 180 °C, the formyl group of the solvent DMF was incorporated in the aliphatic secondary amine side-chain of **26** to form **27** (80%, Scheme 56). When the reaction was done at 210 °C in NMP, even the pyrrolidine ring of NMP was cleaved and was added to the secondary amine nitrogen (not shown in Scheme 56).




Scheme 56: Doubly prenylated indole **26** did not undergo any prenyl shift under microwave irradiation.

No clean products were formed under microwave conditions when the structural isomer **177** was exposed to 0.5 equivalents of TFA in toluene at 150 °C for 15 min (Scheme 57). Some of the isolated fractions showed 3 fold excess signals in the $^{13}C$

NMR spectrum with very broad signals in the $^1$H NMR spectrum, probably being polymerized.

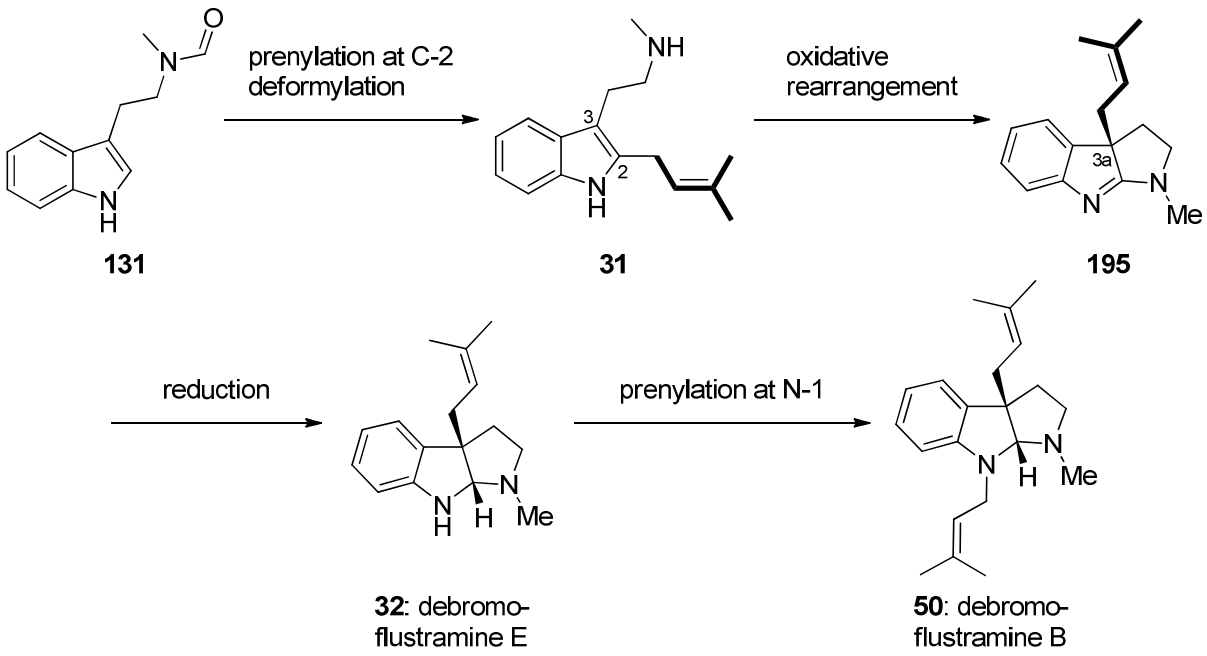



**177**

Scheme 57: Indole **177** formed unseparable complex mixtures under microwave conditions.

### 3.8 Studies towards the total synthesis of debromoflustramine E

Based on the experimental experience with NBS-induced rearrangements on 2-*tert*-prenyltryptamines, it is speculated that a regularly prenylated derivative **31** may furnish the oxidized version of debromoflustramine E (**195**) which upon reduction of the imine bond of tricyclic compound **195** would result in the synthesis of debromoflustramine E (**32**). Additional prenylation at the indolic nitrogen may afford debromoflustramine B (**51**, Scheme 58).




**131** **31** **195**

**32**: debromo-flustramine E

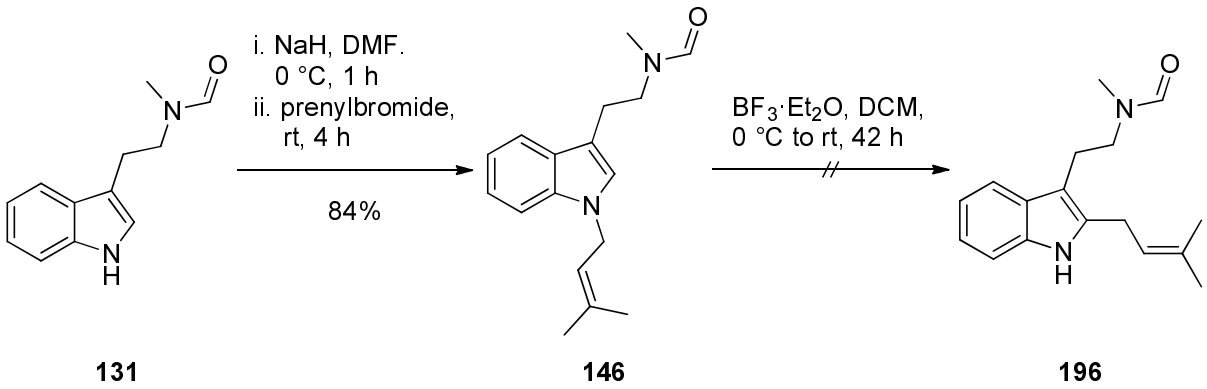
**50**: debromo-flustramine B

Scheme 58: Possible synthetic route to debromoflustramine E (**32**) and B (**51**).

Once more, $N_b$-formyl-$N_b$-methyltryptamine (**131**) served as starting material towards the synthesis of directly prenylated natural product analogues. The initial target was to introduce a regular prenyl group at the indole 2-position of **131**.

### 3.8.1 Installation of a regular prenyl group at the indole 2-position

The N-prenylation of $N_b$-formyl-$N_b$-methyltryptamine (**131**) led to 1-(3,3-dimethylallyl)-$N_b$-formyl-$N_b$-methyltryptamine (**146**). However, the attempted rearrangement of **146** using $BF_3 \cdot Et_2O$ in DCM did not result in the 2-prenylated product **196**. Although the TLC showed several spots, efforts to obtain any of the pure compounds were not fruitful. Compound **196** was unstable at room temperature and degradation of **196** was observed (Scheme 59).[25]




Scheme 59: $BF_3 \cdot Et_2O$ did not induce rearrangement of the N-prenyl group.

Similar attempts were made on the structurally related, phthalimide-protected compound **165**. Treatment of **165** with NaH and prenylbromide resulted in the conversion to $N_a$-prenylated phthalimide protected indole **208** in good yields. For compound **208** an X-ray crystal structure was also obtained (Figure 23).

When **208** was treated with $BF_3 \cdot Et_2O$ at –4 °C or 0 °C, rearrangement failed to occur even after 24 hours. The sharp singlet at δ = 6.87 ppm corresponding to 2-H was intact in the $^1$H NMR spectrum and confirmed that rearrangement had not taken place. The starting material **208** was recovered in good amounts (up to 80%, Scheme 62).

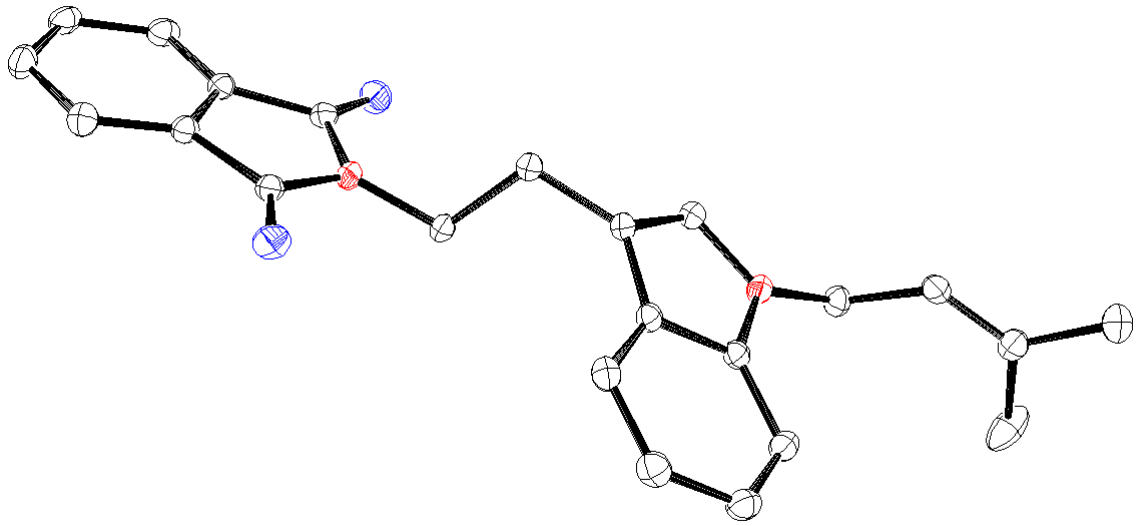
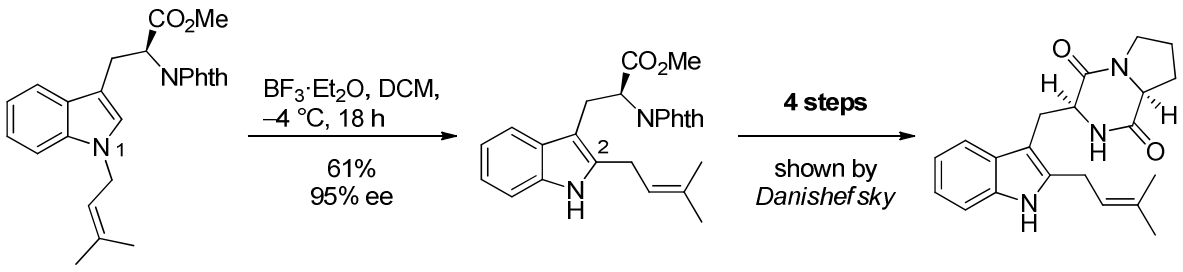


Figure 23: ORTEP drawing of $N_a$-prenyl-phthaloyltryptamine (**208**); hydrogen's are omitted for clarity; displacement parameters drawn at 50% probability.

On the other hand, Cardoso et al. reported this desired rearrangement on a structurally similar molecule, using $BF_3 \cdot Et_2O$. Under optimized conditions, the yield of the product **198** reached up to 61%.[134] Danishefsky and co-workers have reported the total synthesis of tryprostatin B (**199**) starting from this advanced intermediate **198** (Scheme 60).[135]



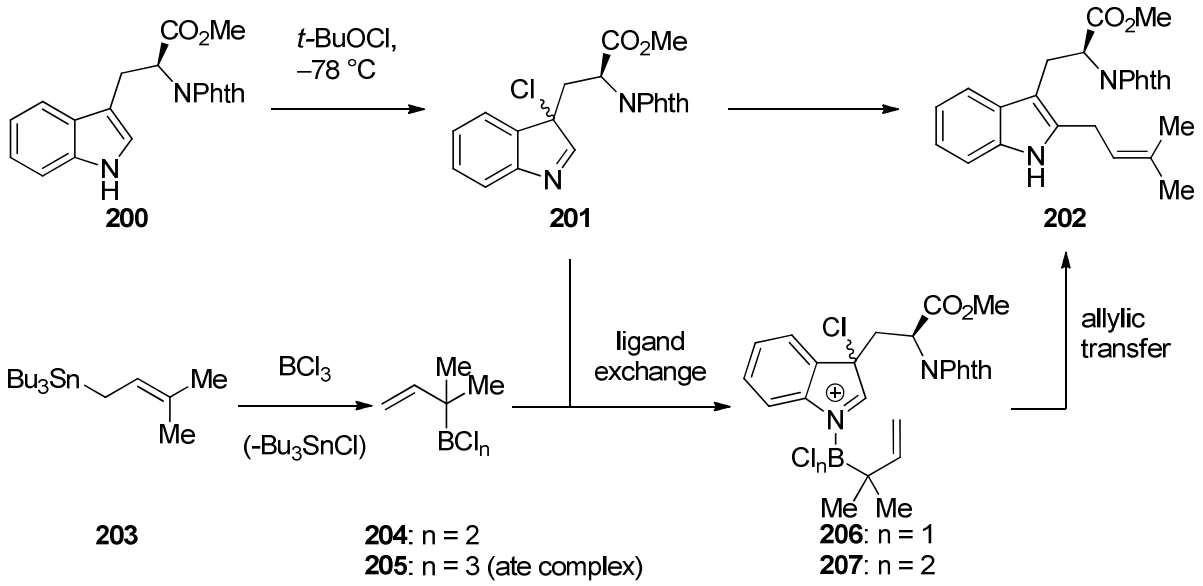

**197** **198** tryprostatin B (**199**)

Scheme 60: Prenyl rearrangement is important for the synthesis of tryprostatin B.[134,135]

As an alternative to the oxidative rearrangements of N-prenylated indoles to 2-prenylindoles, direct introduction of a regular prenyl group was necessary. To install

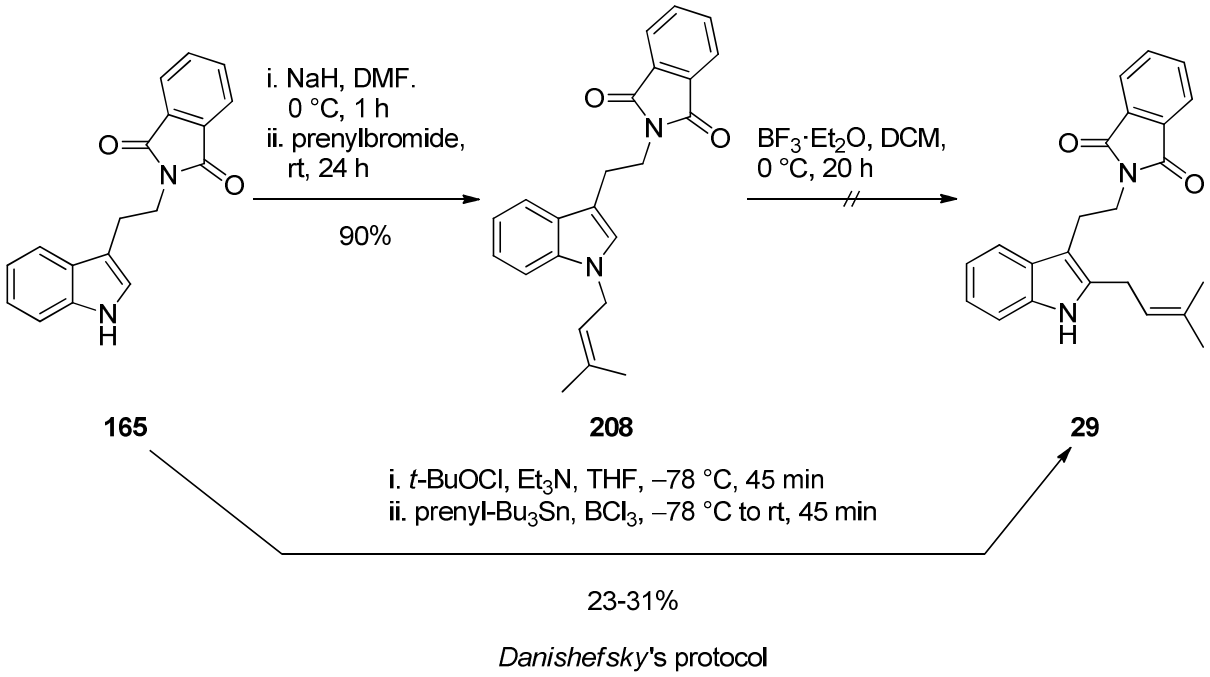
134. A. S. P. Cardoso, M. M. B. Marques, N. Srinivasan, S. Prabhakar, A. M. Lobo, H. S. Rzepa, *Org. Biomol. Chem.* **2006**, *4*, 3966.
135. J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11964–11975.

a regular prenyl group in a single pot process, the protocol developed by Danishefsky et al. was adopted. Towards the total synthesis of tryprostatin B (**199**), Danishefsky et al. designed a new methodology for introducing regular prenyl group at the indole 2-position. In the presence of $NEt_3$, the suitably protected L-tryptophan derivative **200** was reacted with *tert*-BuOCl at –78 °C to generate a chloroindolenine **201**. It was speculated that exposure of prenyl(tri-*n*-butyl)stannane to $BCl_3$ would result in the intermediates **204** and/or **205**. Any of these intermediates **204** and/or **205**, upon reaction with the chloroindolenine **201**, would provide **206**. This advanced chloroindolenine **206**, finally underwent allyl rearrangement furnishing the 2-prenylated indole **202** in good yield (Scheme 61).[135]




Scheme 61: Danishefsky's prenyl group installation at the indole 2-position.[135]

Phthalimide protected tryptamine (**165**) was reacted with *tert*-BuOCl (**137**) in presence of $NEt_3$ at –78 °C for 45 min to produce the chloroindolenine. Addition of prenyl(tri-*n*-butyl)stannane followed by rapid addition of $BCl_3$ within 2 min and stirring further for 45 min gave the desired prenylated indole **29** (Figure 24 and Figure 25) with yields ranging from 23 to 31% (Scheme 62).




Scheme 62: Synthesis of an indole derivative functionalized with a direct prenyl moiety at indole C-2.

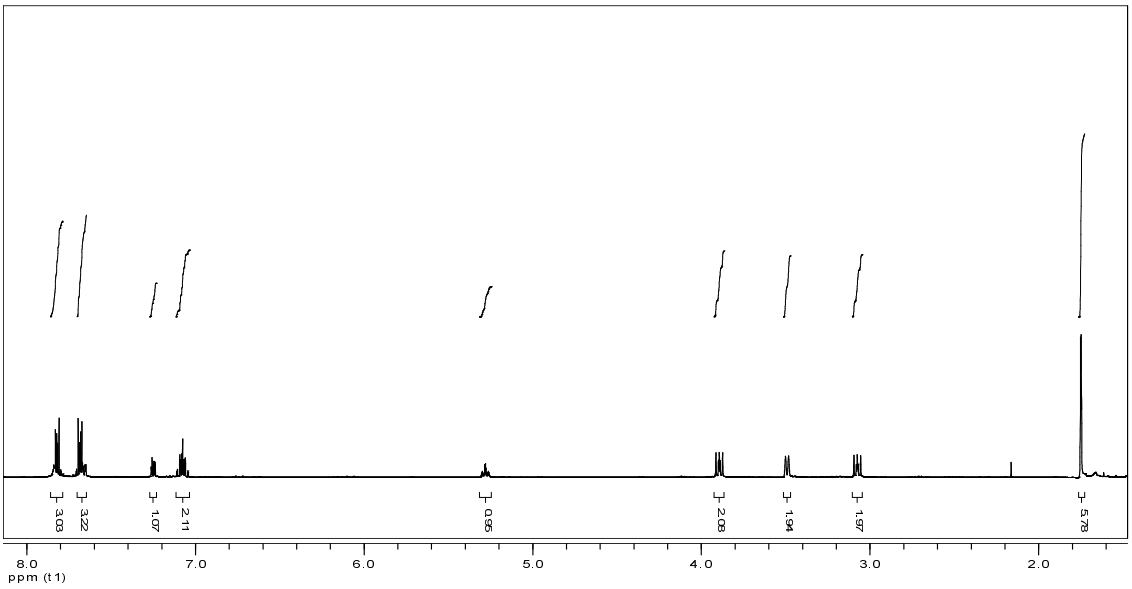



Figure 24: $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **29**.

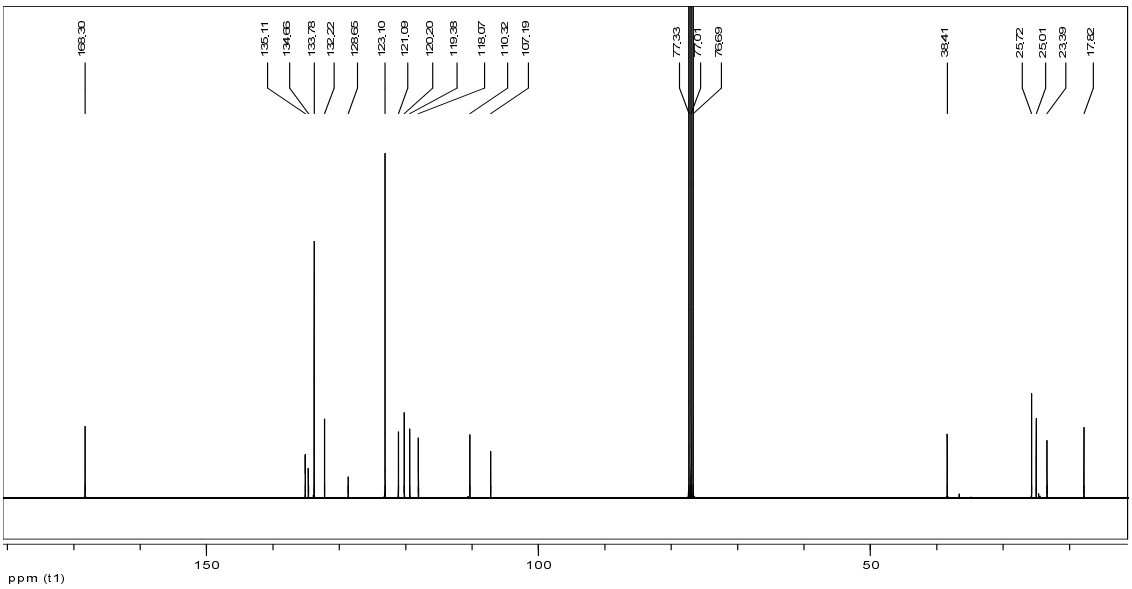
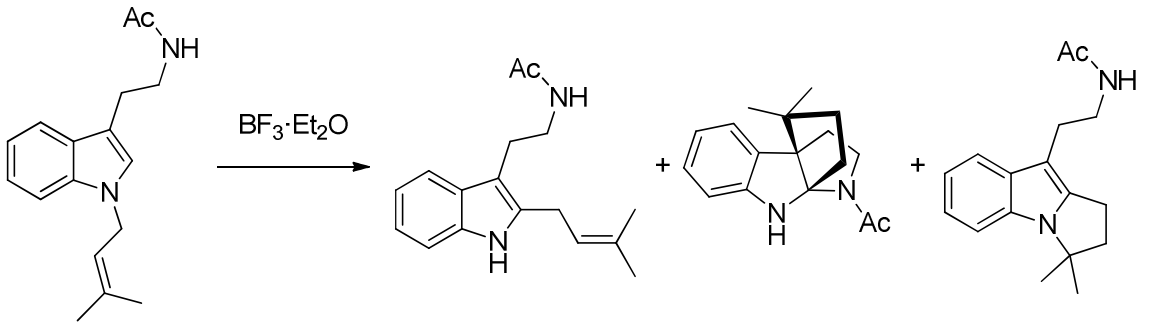



Figure 25: $^{13}C$ NMR spectrum (100 MHz, $CDCl_3$) of compound **29**.

Optimization of this step by varying the temperature, reaction time, addition rates of reagents, and number of equivalents of $BCl_3$ and prenylstannane did not improve the yield. Although the TLC indicated a good conversion, the efforts to isolate the desired compound **29** were unsuccessful. Removal of excess amounts of prenyl(tri-*n*-butyl)stannane reagent proved to be difficult and substantial amounts of product were lost during chromatography even on a silica gel column loaded with 10% KF (w/w). The directly prenylated compound **29** was stable indefinitely as an orange amorphous solid whereas it degraded to a mixture of unknown compounds in solution state.

Cardoso and co-workers mentioned in their publication that the N-prenyl group underwent migration to 2-prenylindole **210** which reacted further with $BF_3{\cdot}Et_2O$ to afford **211** and **212** (Scheme 63).[136]

136. A. S. Cardoso, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **2000**, *41*, 3611–3613.




**209** **210** **211** **212**

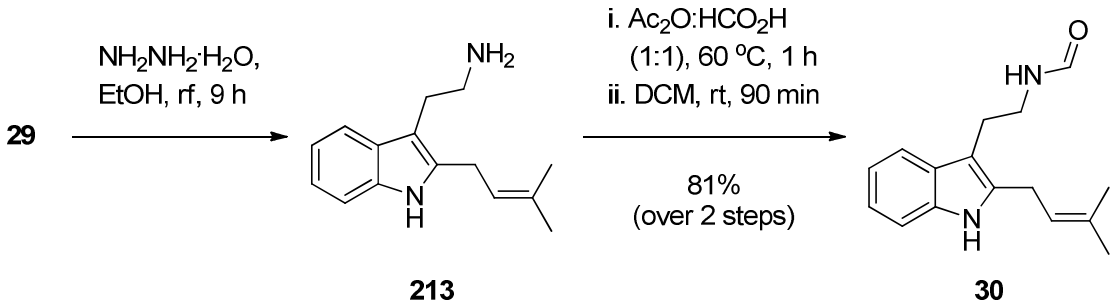
Scheme 63: 2-Prenylindole **210** reacted further to afford **211** and **212**.[136]

Regularly prenylated at C-2, compound **29** could be envisaged as starting material towards the synthesis of advanced precursors for flustramine E (**50**) and flustramine B (**41**). The focus was turned onto the conversion of the phthalimide protected ethylamine side chain of **29** to a methyl substituted secondary amine.

### 3.8.2 Synthesis of 2-prenyl-methyltryptamine

Removal of the phthalimide group was effected by treating indole **29** with excess hydrazine monohydrate in MeOH/DCM (1:1) at room temperature. After two days, the desired amine **213** was obtained in moderate yield (46%). Changing the solvent system to EtOH and by refluxing for 9 h[124] afforded negligible improvement (49%). However, refluxing for 24 h in the presence of 12.0 equivalents of hydrazine monohydrate gave the desired product **213** in the best yield of 82%.

Application of Bosch conditions on the amine **213** afforded the 2-prenyl-$N_b$-formyltryptamine (**30**). A mixture of $Ac_2O$ and $HCO_2H$ was stirred at 60 °C for 1 h. A solution of **213** in DCM was added to the acidic mixture at room temperature and stirred for 90 min to furnish the formylindole **30** in an excellent yield of 99% (Scheme 64) requiring no further purification (Figure 26 and Figure 27).




Scheme 64: Synthesis of 2-prenyl-$N_b$-formyltryptamine (**30**).

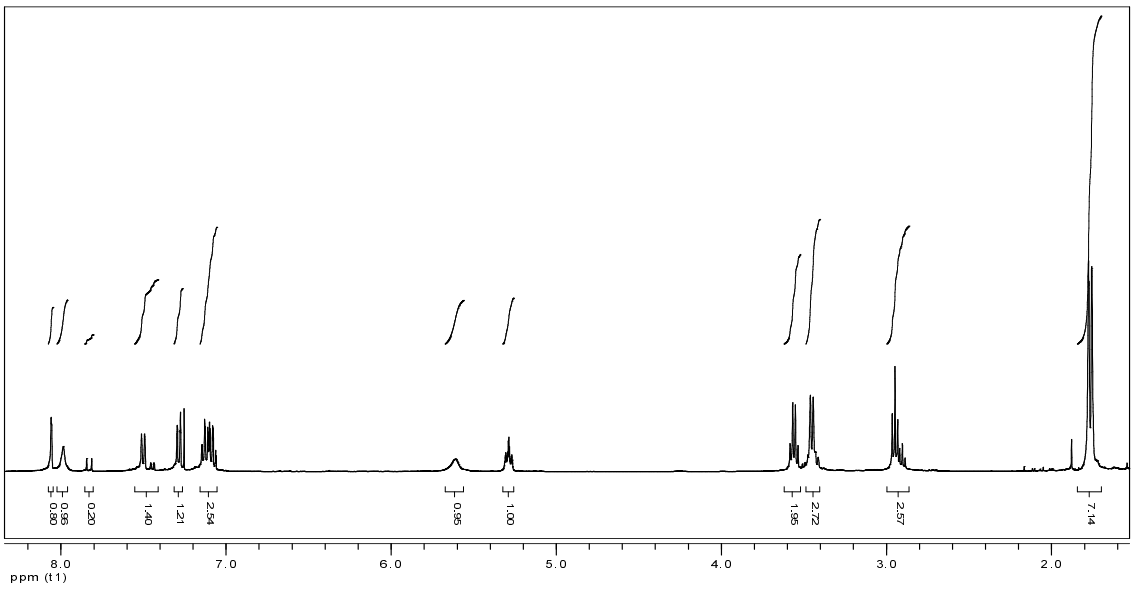



Figure 26: $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound **30**.

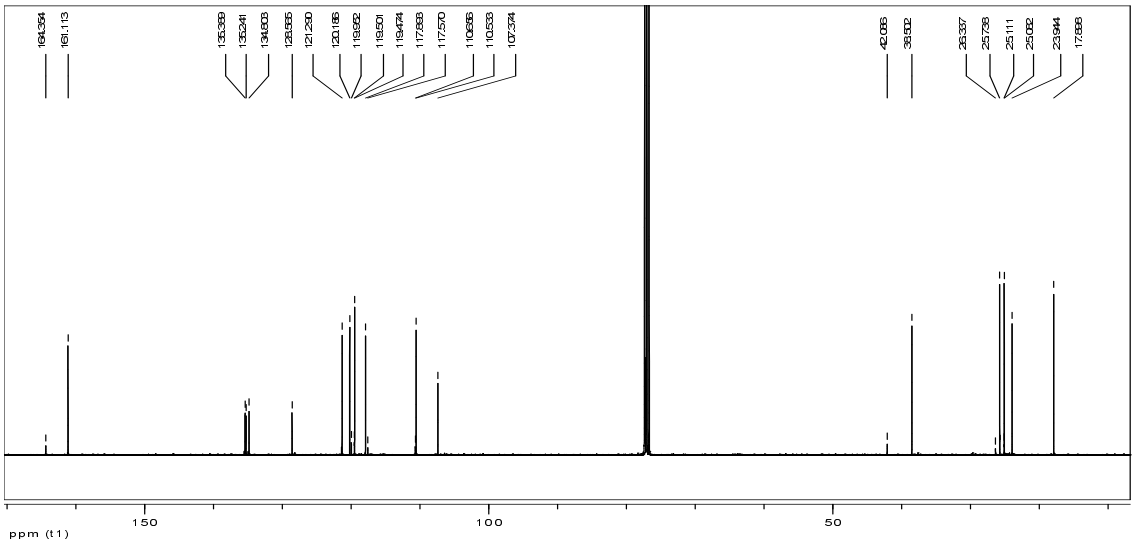
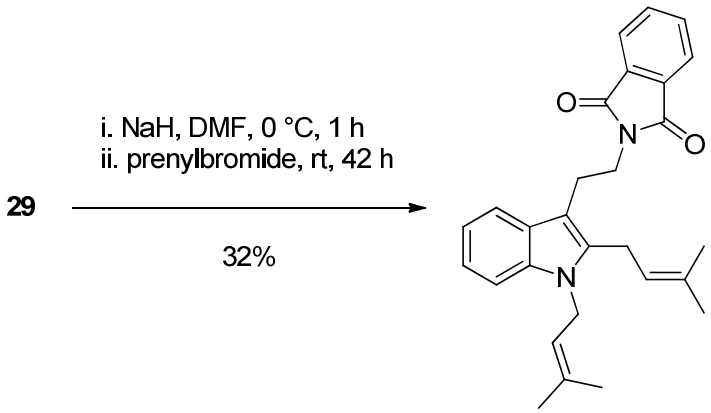



Figure 27: $^{13}$C NMR spectrum (100 MHz, $CDCl_3$) of compound **30**.

Compound **30** was reacted with 4.2 equivalents of DIBAL-H at room temperature for 24 hours. Column chromatography of the resulting crude reaction mixture led to the

isolation of the desired product, but the NMR spectrum of **31** showed impurities. The low resolution GC-EI-MS analysis indicated a molecular ion peak at 240 confirming the presence of the desired **31** as a major product. Repeated column chromatography including reversed phase HPLC did not afford the pure compound, either. The TLC of the isolated spots was neither stable nor reproducible.

Compound **29** was prenylated for the second time to obtain **214**. The doubly prenylated **214** is also a potential structural phthalimide isomer to **Li-0097** and **Li-0098** for evaluation of biological activity. Behaving in similar manner as in the case of prenylation on **166** and **2**, compound **29** afforded the doubly prenylated indole **214** in an isolated yield of 32% (Scheme 65). Under standard GC conditions (see Section 4.1) **214** did not elute from the GC column.




**214**

Scheme 65. Synthesis of doubly prenylated indole **214**.

### 3.9 Biological activity

*Flustra* alkaloids and synthetic derivatives were tested against microorganisms, quorum sensing, bacterial biofilm, ion channels, acetylcholine receptors and cholinesterase targets (see Section 2.3). They showed activity against a wide range of biological targets indicating that these natural products and analogues have great potential towards medicinal applications. Extensive screening of prenylated indole alkaloids and derivatives was not investigated before. A thorough biological evaluation with respect to cytotoxicity, specific antimicrobial activities and biofilm formation inhibitions was needed.

Given the broad extent of biological activities, evaluation of 30 indole derivatives (Figure 28 and Figure 29) including natural products $N_b$-methyltryptamine (**Li-78**), $N_b$-formyl-$N_b$-methyltryptamine (**Li-21**), and *Flustra* alkaloids flustrabromine (**Li-23**), deformylflustrabromine (**Li-67**), flustramine C (**Li-68**), and dihydroflustramine C (**Li-69**) was performed. Most of the synthetic derivatives and intermediates were *Flustra* analogues with varying substitution patterns, functionalized with one or two prenyl or *tert*-prenyl groups. Figure 28 and Figure 29 give the structures of the indole derivatives tested for cytotoxicity, antimicrobial activity, and inhibition of biofilm formation. Figure 29 depicts the structures of phthalimide protected tryptamines functionalized with mono- and/or double prenyl groups at the pyrrole section.

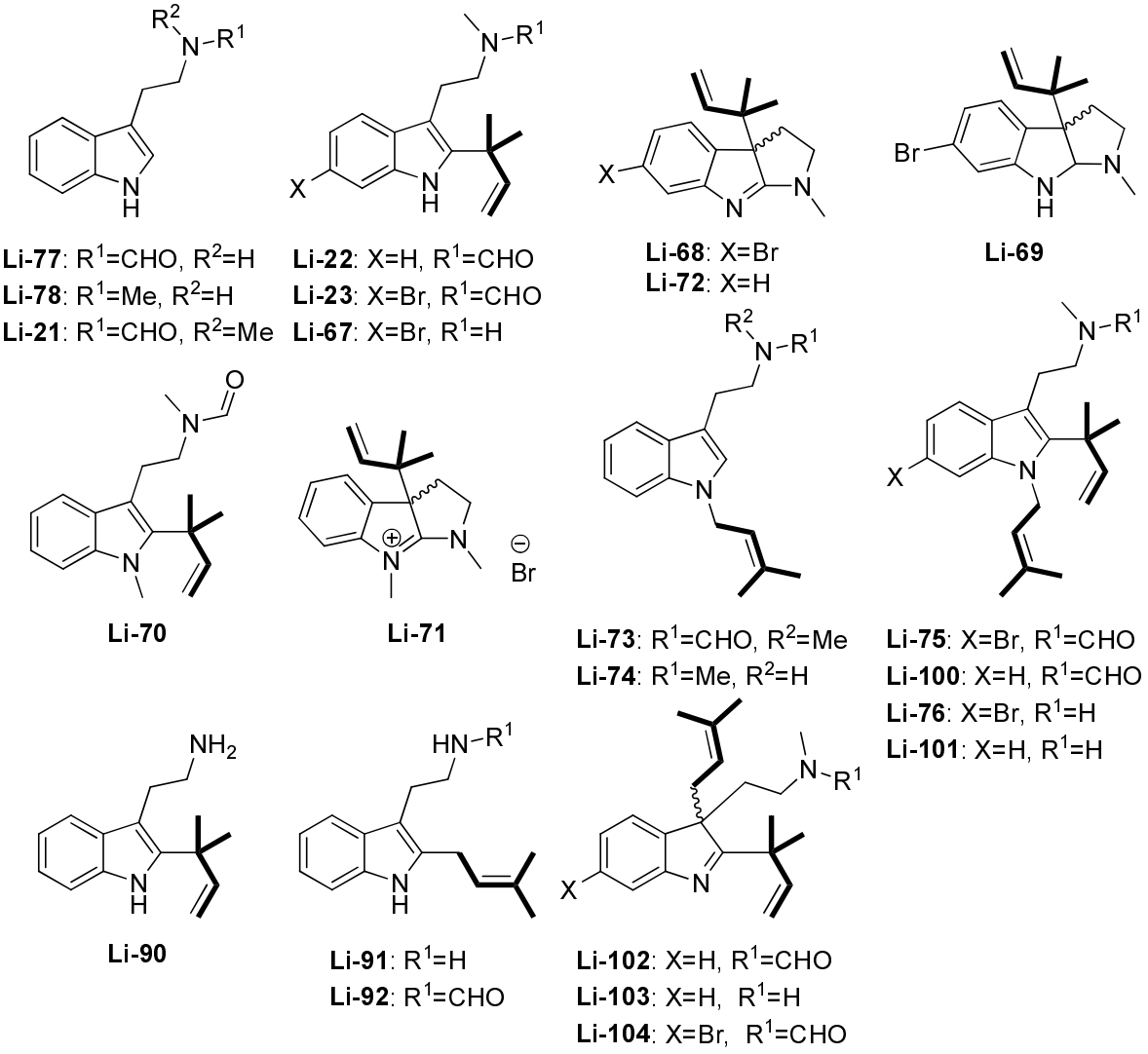



Figure 28: Structures of biologically evaluated flustramine-type compounds (The numbers are adapted from the compound library maintained at Lindel group).

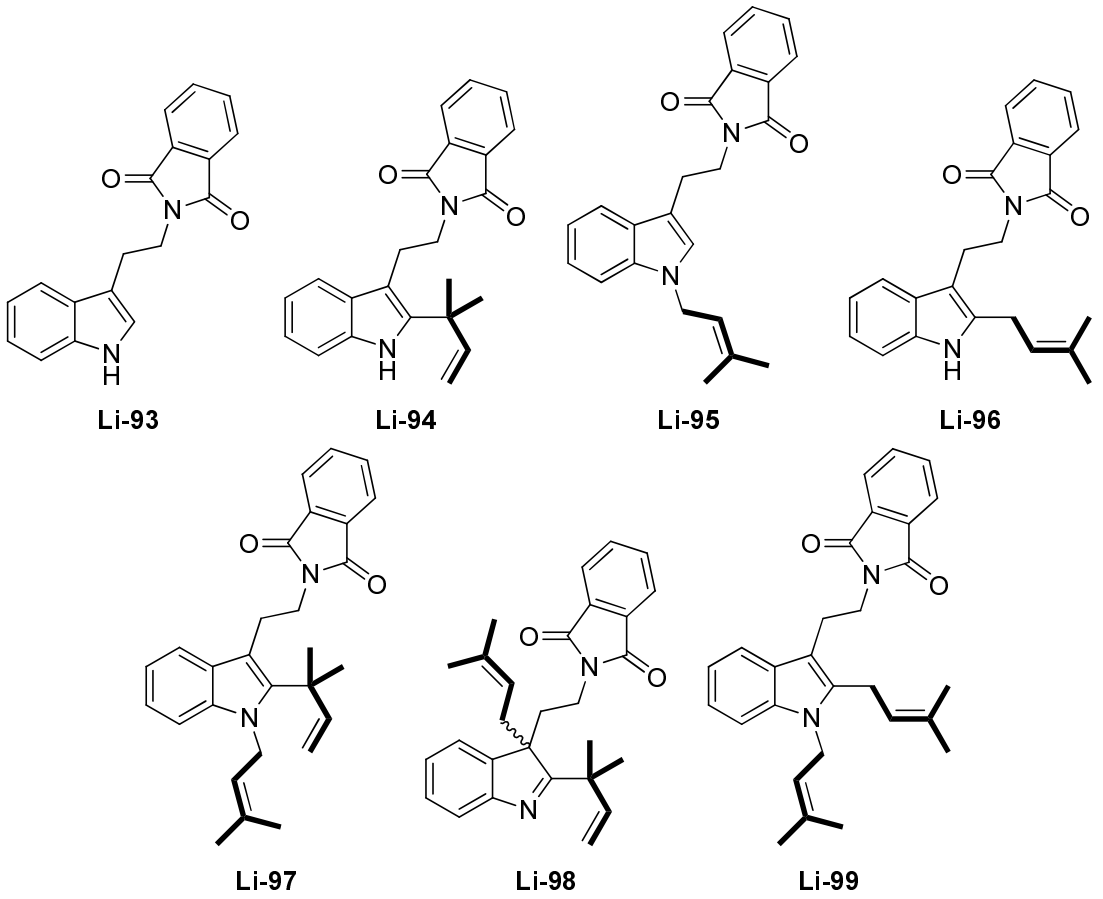



Figure 29: Mono- and doubly prenylated phthalimides were evaluated for biological activity (The numbers are adapted from the compound library maintained at Lindel group).

### 3.9.1 Cytotoxicity

#### 3.9.1.1 *In vitro* evaluation against human cancer cell lines

The cytotoxicity evaluation was performed by Prof. Dr. Fiebig and co-workers at Oncotest GmbH, Freiburg (Germany). The cancer cell lines were derived from tumors of stomach, lung, breast, melanoma, ovary, pancreas, prostate, mesothelioma, kidney, and uterus. The preliminary *in vitro* cytotoxicity evaluation was carried out against twelve cell lines of ten different cancer types.

During the preliminary examination, a total of 30 molecules were tested at five different concentrations. The compounds exhibiting cytotoxicity under 25 µM were screened thoroughly against a panel of 42 different human cancer cell lines (Table 7, Table 8 and Table 9). In the tables, compounds exhibiting $IC_{50}$ values ranging

between 0–25 µM are colored in green, 25–50 µM in yellow and 50–99 µM in blue whereas 100–above µM cytotoxicity values are not colored.

$N_b$-formyl-$N_b$-methyltryptamine (**Li-21**), $N_b$-formyltryptamine (**Li-77**), $N_b$-methyltryptamine (**Li-78**), and phthaloyltryptamine (**Li-93**) showed no cytotoxicity. Deformylflustrabromine (**Li-67**) was cytotoxic against the colon cancer cell line CXF-HT29 ($IC_{50}$=12.3 µM) and lung cancer cell lines LXFA–629 and LXFL–529 ($IC_{50}$=12.9 and 12.8 µM, respectively). Flustramine C (**Li-68**) showed a geometric mean $IC_{50}$ value of 37.3 µM with sensitivity only against the lung cancer cell line LXFL–529 ($IC_{50}$=21 µM). Dihydroflustramine C (**Li-69**) showed much better activity than **Li-68** with good selectivity against colon cancer cell line CXF–HT29 and lung cancer cell line LXFA–629 with $IC_{50}$ values of 8.8 and 12.9 µM, respectively. N-prenylated secondary amine **Li-74** showed good sensitivity to colon cancer cell line CXF–HT29 ($IC_{50}$=9.1 µM) whereas flustrabromine (**Li-23**) was only cytotoxic to lung cancer cell line LXFL–529 ($IC_{50}$=12.1 µM). Very weak cytotoxicity was observed for synthetic indoles **Li-70**, **Li-71**, debromoflustramine C (**Li-72**), N-prenylated **Li-73**, and debromoflustrabromine (**Li-22**).

The best cytotoxicity was exhibited by the doubly prenylated $N_a$-prenyl-flustrabromine (**Li-75**) and $N_a$-prenyl-deformylflustrabromine (**Li-76**) with geometric mean $IC_{50}$ values of 12.4 and 3.8 µM, respectively. Presence of a second prenyl group in the case of **Li-76** increased the cytotoxicity by a factor of six, when compared to **Li-67**. Debromo analogues **Li-100** and **Li-101** also showed good cytotoxicity (geometricmean $IC_{50}$ values of 22.6 and 3.76 µM, respectively).

Weak activity was recorded for 2-prenyl-$N_b$-formyltryptamine (**Li-92**), and C-3 prenylated **Li-102** and **Li-104**. Replacement of a formyl group by a hydrogen caused a two-fold increment in activity in case of **Li-103** compared to **Li-102**. Structural isomers **Li-90** and **Li-91** possessed similar cytotoxicity.

An interesting trend was observed for phthalimide protected tryptamines (**Li-93 – Li-99**). **Li-93** did not show any activity. 2-*Tert*-prenylindole **Li-94** possessed good activity (geometric mean $IC_{50}$=25.4 µM) whereas N-prenylated structural isomer **Li-95** was weakly active (geometric mean $IC_{50}$= 53.9 µM). 2-Prenylindole **Li-96** was more active against stomach GXF–251($IC_{50}$=8.3 µM) and showed better activity than **Li-94** and **Li-95**. Interestingly, 1,2-diprenylated indoles **Li-97** and **Li-99** showed no

significant cytotoxicity (geometric mean $IC_{50}$=45.9 and 62.8 µM, respectively) than 2,3-diprenylated indole **Li-98** (geometric mean $IC_{50}$ = 16.7 µM).

Table 7: Proliferation inhibition of human cancer cell lines by indole derivatives.

| Cancer type | type | name | Li-67 | Li-68 | Li-69 | Li-70 | Li-71 | Li-72 | Li-73 | Li-74 | Li-75 | Li-76 | Li-22 | Li-23 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Stomach** | CXF | HT29 | 12.3 | 34 | 8.76 | 49.8 | 42.4 | 48.1 | 42.5 | 9.1 | 11.7 | 2.43 | 100 | 100 |
| **Stomach** | GXF | 251 | 31.7 | 39.6 | 32.6 | 38.1 | 80 | 100 | 80 | 34.5 | 12.9 | 4.15 | 80 | 100 |
| **Lung** | LXFA | 629 | 12.9 | 41.2 | 12.9 | 52.3 | 100 | 87.1 | 80 | 13.8 | 12.8 | 3.12 | 100 | 100 |
| **Lung** | LXFL | 529 | 12.8 | 21 | 18.7 | 49 | 46.9 | 59.4 | 51.6 | 14.5 | 9.83 | 3.41 | 58.6 | 12.1 |
| **Melanoma** | MEXF | 462 | 41.5 | 40.5 | 75.5 | 47.6 | 41.7 | 100 | 68.5 | 78.2 | 14.6 | 12.4 | 100 | 100 |
| **Ovary** | OVXF | 899 | 16 | 45 | 29.2 | 68.8 | 100 | 97.3 | 100 | 17 | 13.2 | 3.66 | 100 | 100 |
| **Pancreas** | PAXF | 1657 | 29.4 | 58.7 | 44.8 | 91.9 | 87.9 | 100 | 87.6 | 41.1 | 16 | 3.55 | 100 | 100 |
| **Prostate** | PRXF | 22Rv1 | 21.1 | 30.8 | 16.7 | 44.6 | 27.7 | 37.3 | 57 | 23.1 | 8.49 | 2.99 | 50.6 | 100 |
| **Mesothe-lioma** | PXF | 1752 | 18.3 | 36 | 15.7 | 38 | 59.7 | 87.4 | 62 | 17.1 | 16.4 | 3.33 | 100 | 100 |
| **Kidney** | RXF | 486 | 22.8 | 49.8 | 38.4 | 100 | 100 | 100 | 100 | 42.6 | 11.8 | 3.73 | 100 | 100 |
| **Uterus** | UXF | 1138 | 19.7 | 28.2 | 37.2 | 41.8 | 43.7 | 100 | 80 | 47.7 | 10.9 | 3.71 | 80 | 100 |
| **Geometric mean $IC_{50}$ =** | | | **20.1** | **37.3** | **25.1** | **53.6** | **60.8** | **79.4** | **71.2** | **25.3** | **12.4** | **3.8** | **86** | **82.6** |

Table 8: Proliferation inhibition of human cancer cell lines by indole derivatives.

| Cancer type | type | name | Li-90 | Li-91 | Li-92 | Li-94 | Li-95 | Li-96 | Li-97 | Li-98 | Li-99 | Li-100 | Li-101 | Li-102 | Li-103 | Li-104 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stomach | CXF | HT29 | 37.2 | 32 | 82.1 | 23.3 | 28.9 | 15.1 | 42.7 | 16.2 | 65.1 | 17.1 | 2.95 | 64.8 | 13.9 | 71.9 |
| Stomach | GXF | 251 | n.e. | 27.4 | 44.2 | 16.1 | 24.4 | 8.3 | 24.1 | 16.1 | 36.1 | 21 | 3.96 | 69.4 | 29 | 55.3 |
| Lung | LXFA | 629 | n.e. | 43.8 | 73.6 | 40.2 | 87.8 | 22.2 | 100 | 28.8 | 100 | 37.9 | 3.64 | 96.7 | 20 | 51.5 |
| Lung | LXFL | 529 | 39.1 | 49.4 | 81.2 | 21.9 | 34.5 | 13.7 | 36.6 | 15.1 | 44.1 | 29.6 | 4.68 | 51.7 | 38 | 37.7 |
| Breast | MAXF | 401 | n.e. | 39.4 | 86.4 | 19.9 | 47.1 | 17.8 | 38 | 14.2 | 100 | 22.6 | 3.20 | 48.4 | 23.9 | 40.8 |
| Melanoma | MEXF | 462 | 83.4 | 77.2 | 100 | 45.5 | 100 | 48.5 | 52.4 | 15.4 | 100 | 16.7 | 5.01 | 60.2 | 37.8 | 50.3 |
| Ovary | OVXF | 899 | 49.4 | 75.7 | 100 | 30.2 | 100 | 27 | 31.8 | 19.5 | 100 | 22.1 | 4.26 | 59.5 | 20.5 | 42 |
| Pancreas | PAXF | 1657 | 67.8 | 60.3 | 100 | 32 | 100 | 23.7 | 100 | 33.3 | 100 | 37.8 | 4.46 | 100 | 41.6 | 70 |
| Prostate | PRXF | 22Rv1 | 40.9 | 44.4 | 100 | 16.7 | 34.8 | 17.9 | 32.1 | 11.2 | 39.2 | 15.6 | 3.59 | 42.6 | 30.8 | 45.7 |
| Mesothe-lioma | PXF | 1752 | 54.8 | 46.7 | 100 | 36.4 | 43.6 | 28.7 | 46.4 | 15.3 | 62.6 | 29.5 | 3.94 | 66.7 | 23.9 | 70 |
| Kidney | RXF | 486 | 61.4 | 50.1 | 100 | 29.8 | 78.8 | 32.9 | 25.2 | 15.4 | 41.1 | 20.2 | 3.17 | 41.2 | 15.1 | 32.7 |
| Uterus | UXF | 1138 | 41.7 | 77.1 | 100 | 14 | 49.9 | 19.8 | 98.3 | 10.8 | 36 | 14.6 | 2.90 | 39.8 | 23.7 | 33.6 |
| **Geometric mean $IC_{50}$ =** | | | **51** | **49.4** | **87** | **25.4** | **53.9** | **20.9** | **45.9** | **16.7** | **62.8** | **22.6** | **3.76** | **59.1** | **25.1** | **48.3** |

Among the 30 tested compounds, **Li-67**, **Li-68**, $N_a$-prenyl-2-H indole **Li-74**, doubly prenylated **Li-75** and **Li-76** were evaluated for cytotoxicity against a panel of 42 human cancer cell lines (Table 9).

Deformylflustrabromine (**Li-67**) showed good cytotoxicity against colon cancer cell lines CXF–DIFI ($IC_{50}$ = 12.6 µM) and CXF–RKO ($IC_{50}$ = 13.8 µM). Compound **Li-67** also showed activity on lung tumor cell line LXFA–629L ($IC_{50}$ = 13.4 µM), breast cancer cell line MAXF–401NL ($IC_{50}$ = 12.1 µM), and melanoma tumor cell line MEXF–1341L ($IC_{50}$ =13.7 µM), respectively. Flustramine C (**Li-68**) was cytotoxic to only prostate cancer cell line PRXF–LNCAP ($IC_{50}$= 13.6 µM). Slightly more active than **Li-68** was the N-1-prenyl-2-H indole **Li-74** with $IC_{50}$ values of 10.6 and 13.7 µM against colon cancer cell line CXF–HT29 and lung cancer cell line LXFA-629L, respectively.

Doubly prenylated **Li-75** showed excellent cytotoxicity towards colon cancer cell line CXF–HT29, lung cancer cell line LIXF–575L, breast cancer cell line MAXF–401NL, and prostate cancer cell line PRXF–LNCAP with $IC_{50}$ values of 14.9, 12.8, 12.8, and 4.14 µM, respectively). However, $N_a$-prenyl-deformylflustrabromine (**Li-76**) was more active (geometric mean $IC_{50}$ = 5.1 µM) than any other indole tested from the series. Against 28 different cancer cell lines, **Li-76** showed $IC_{50}$ values below 4.8 µM. The best $IC_{50}$ values of 1.88 and 2.41 µM were recorded against lung cancer cell line LXFA–629L and breast cancer cell line MAXF-401NL, respectively.

Table 9: Antitumor activity of **Li-67**, **Li-68**, **Li-74**, **Li-75**, and **Li-76** against 42 human cancer cell lines.

| Cancer type | type | name | Li-67 | Li-68 | Li-74 | Li-75 | Li-76 |
|---|---|---|---|---|---|---|---|
| **Bladder** | BXF | 1218L | 39.9 | 48 | n.e. | 21.3 | 3.7 |
| | BXF | 1352L | 33.6 | 47.8 | 47.3 | 33 | 9.51 |
| | BXF | T24 | 58.7 | 83 | 82.3 | 22.3 | 9.64 |
| **Colon** | CXF | 269L | 21 | 38.7 | n.e. | 22 | 3.89 |
| | CXF | DIFI | 12.6 | 40.5 | 30.2 | 16.4 | 3.78 |
| | CXF | HCT116 | 27.5 | 46.2 | 39.6 | 15.8 | 3.92 |
| | CXF | HT29 | 16.4 | 46.6 | 10.6 | 14.9 | 3.55 |
| | CXF | RKO | 13.8 | 42.1 | 18.5 | 15.5 | 3.98 |
| **Stomach** | GXF | 251L | 31.4 | 39.1 | 29.9 | 19.6 | 3.23 |

| Cancer type | type | name | Li-67 | Li-68 | Li-74 | Li-75 | Li-76 |
|---|---|---|---|---|---|---|---|
| | GXF | MKN45 | 48.4 | 36.3 | 40.5 | 31.6 | 4.83 |
| **Throat-head** | HNXF | CAL27 | 41.8 | 42.3 | 49.1 | 25.5 | 3.76 |
| **Lung** | LXF | 575L | n.e. | 23.2 | n.e. | 12.8 | n.e. |
| | LXF | H460 | 36 | 49.9 | 35.4 | 29.1 | 12.9 |
| | LXFA | 289L | 18.1 | 38.4 | n.e. | 23 | 10.7 |
| | LXFA | 526L | 35.7 | 39.7 | 38.8 | 29.7 | 3.74 |
| | LXFA | 629L | 13.4 | 37 | 13.7 | 15.2 | 1.88 |
| | LXFL | 1121L | 30.5 | 40.2 | n.e. | 18.4 | 12.1 |
| | LXFL | 529L | 27 | 32.2 | 31.7 | 19.7 | 3.75 |
| **Breast** | MAXF | 401NL | 12.1 | 29.5 | 22.9 | 12.8 | 2.41 |
| | MAXF | MCF7 | 21.5 | 38.5 | 20.8 | 15.8 | 14.5 |
| | MAXF | MDA231 | 36.7 | 56.2 | 41.7 | 32 | 12.8 |
| **Melanoma** | MEXF | 1341L | 13.7 | 36.6 | n.e. | 17.2 | 3.88 |
| | MEXF | 276L | 41.2 | 51.3 | 46.3 | 22.9 | 8.99 |
| | MEXF | 462NL | 56.7 | 62.7 | 48.8 | 25.5 | 8.09 |
| **Ovary** | OVXF | 899L | 28.3 | 47.2 | 39.6 | 15.9 | 10.3 |
| | OVXF | OVCAR3 | 47.9 | 77 | 77 | 28.5 | 10.8 |
| **Pancreas** | PAXF | 1657L | 57.8 | 88.9 | 51.4 | 48.9 | 6.88 |
| | PAXF | 546L | 30.2 | 37.3 | 40.7 | 32.4 | 11.3 |
| | PAXF | PANC1 | 40.9 | 59.6 | 49.8 | 21.4 | 3.79 |
| **Prostate** | PRXF | 22RV1 | 46.3 | 51 | 51.8 | 17.2 | 3.66 |
| | PRXF | DU145 | 39.9 | 47.3 | 42.5 | 24.5 | 3.88 |
| | PRXF | LNCAP | 31.5 | 13.6 | 21.7 | 4.14 | 5.82 |
| | PRXF | PC3M | 29.7 | 41.2 | 43.1 | 18.2 | 4.01 |
| **Mesothelioma** | PXF | 1118L | 28.3 | 51.6 | 45.9 | 48.1 | 3.91 |
| | PXF | 1752L | 44 | 39.7 | 39.1 | 29.2 | 3.81 |
| | PXF | 698L | 42.6 | 50.6 | 37.9 | 46 | 3.84 |
| **Kidney** | RXF | 1781L | 30.9 | 46.5 | 37.1 | 15.5 | 3.4 |
| | RXF | 393NL | 44.6 | 37.9 | 45.4 | 21.7 | 3.71 |
| | RXF | 486L | 23.9 | 50.1 | 31.5 | 21.2 | 3.72 |
| **Sarcoma** | SXF | SAOS2 | 47.3 | 63.5 | 48 | 23.5 | 4 |
| | SXF | TE671 | 51.3 | 38 | 51.9 | 22.6 | 4.02 |
| **Uterus** | UXF | 1138L | 16.6 | 27.7 | 24.5 | 15.7 | 3.38 |

| Cancer type type name | Li-67 | Li-68 | Li-74 | Li-75 | Li-76 |
|---|---|---|---|---|---|
| **Geometric mean $IC_{50}$ =** | **30.5** | **43.4** | **36.7** | **21.2** | **5.14** |

In summary, open chain prenylindoles appear to be more cytotoxic than pyrrolo[2,3-*b*]indoles. Doubly prenylated indoles showed higher cytotoxicity than the corresponding mono prenyl indoles which, in turn, are more cytotoxic than non-prenylated indoles. The effect of presence/absence of bromine for cytotoxicity is unclear whereas the formyl group diminished cytotoxicity.

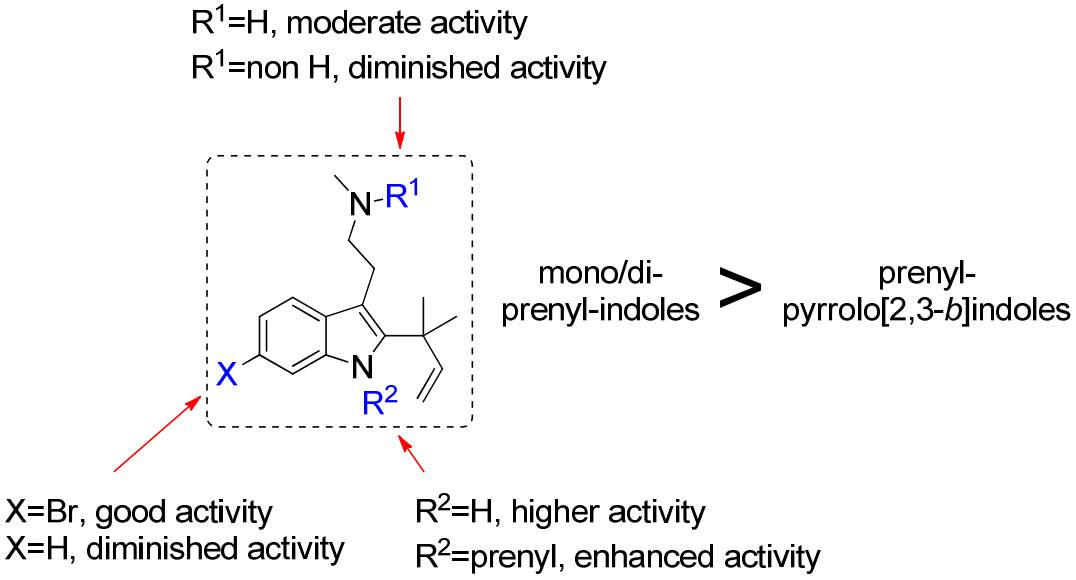



Figure 30: SAR summary of prenylated indoles.

### 3.9.1.2 MTT assay with mouse cell line L-929

Further cytotoxicity evaluation was performed on the mouse fibroblast connective tissue cell line L-929 by Dr. Florenz Sasse and co-workers at the Helmholtz Centre for Infection Research, Braunschweig (Germany).

Among the 30 indole derivatives evaluated, the compounds **Li-67**, **Li-75**, **Li-76**, and **Li-101** exhibited highest cytotoxicity once again. $N_a$-prenyl-deformylflustrabromine (**Li-76**) exhibited an $IC_{50}$ and $IC_{90}$ values of 2.4 and 4 µg/mL, respectively. The debromo analogue **Li-101** showed similar cytotoxicity $IC_{50}$ and $IC_{90}$ values of 2.2, 3.2 µg/mL, respectively (Table 10).

Table 10: Cytotoxicity of 30 indole derivatives was determined in a MTT assay with mouse cell line L-929.

| µg/mL | Li-77 | Li-78 | Li-21 | Li-22 | Li-23 | Li-67 | Li-68 | Li-69 | Li-70 | Li-71 | Li-72 | Li-73 | Li-74 | Li-75 | Li-76 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $IC_{50}$ | 24 | 16 | 14 | 10 | 16 | 8 | 15 | 15 | 16 | 14 | 15 | 15 | 12 | 9 | 2.4 |
| $IC_{90}$ | >40 | >40 | 38 | 38 | >40 | 23 | >>40 | 33 | 39 | 39 | >40 | >40 | 32 | 32 | 4 |

| µg/mL | Li-90 | Li-91 | Li-92 | Li-93 | Li-94 | Li-95 | Li-96 | Li-97 | Li-98 | Li-99 | Li-100 | Li-101 | Li-102 | Li-103 | Li-104 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $IC_{50}$ | 12 | 12 | 20 | 20 | 12 | 23 | 15 | 20 | 18 | 18 | 14 | 2.2 | 18 | 20 | 17 |
| $IC_{90}$ | 40 | 31 | >40 | >40 | 30 | >40 | 30 | 36 | 30 | 40 | 30 | 3.2 | >40 | 32 | 32 |

### 3.9.2 Antimicrobial activity

Collaborative work with Dr. Florenz Sasse and co-workers from the Helmholtz Centre for Infection Research, Braunschweig (Germany) also allowed the determination of antimicrobial activities.

Using agar diffusion assays, the 30 indole derivatives were evaluated for antimicrobial activity against gram positive bacteria *Micrococcus luteus*, *Mycobacterium phlei*, gram negative bacterium *Escherichia coli*-3949, yeast species *Hansenula anomela* and *Saccharomyces cerevisiae* and fungi *Botrytis cinerea*, *Pythium debaryanum*. The test compounds dissolved in methanol were applied onto 6 mm cellulose discs and were allowed to diffuse into the inoculated agar medium. The zones of complete inhibition were determined in mm. Larger zones of complete inhibition correspond to greater antimicrobial activity. Serial dilution assays with bacteria resulted in growth curves from which $IC_{50}$ values of selected compounds were determined.

None of the compounds were antifungal. Only five of the compounds, amidinium salt **Li-71**, $N_a$-prenyl-2-H indole **Li-74**, doubly prenylated $N_a$-prenyl-deformylflustrabromine **Li-76**, debromo analogues **Li-100** and **Li-101** showed greater complete zones of inhibition. **Li-71** and **Li-74** exhibited inhibition zones of 10 mm and 11 mm, respectively against *M. phlei*. **Li-76** showed 13 mm zones of inhibition against each of the *M. luteus*, *M. phlei* and *S. cerevisiae* with corresponding $IC_{50}$ values of 5.9, 7.7, and 17.9 µM, respectively. **Li-100** showed an

8 mm inhibition zone and an $IC_{50}$ value of 23.6 µM against *M. luteus.* The best antimicrobial candidate was debromo-$N_a$-prenyl-deformylflustrabromine (**Li-101**). The zones of inhibitions against *M. luteus*, *M. phlei*, *E. coli*, *H. anomela*, and *S. cerevisiae* were 20, 15, 8, 12, and 12 mm, respectively. An $IC_{50}$ value of 7.7 µM was recorded for **Li-101** against *M. phlei* (Table 11).

Table 11: Antimicrobial evaluation of indoles.

| Microorganism | | Li-71 | | Li-74 | | Li-76 | | Li-100 | | Li-101 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IZ | $IC_{50}$ | IZ | $IC_{50}$ | IZ | $IC_{50}$ | IZ | $IC_{50}$ | IZ | $IC_{50}$ |
| Gram(+)ve Bacteria | *Micrococcus luteus* | - | - | - | - | 13 | 5.9 | 8 | 23.6 | 20 | 22.6 |
| | *Mycobacterium phlei* | 10 | >110 | 11 | 95 | 13 | 7.7 | - | - | 15 | 7.7 |
| Gram(-)ve Bacteria | *E. Coli 3949* | - | - | - | - | - | - | - | - | 8 | 29 |
| Yeast | *Hansenula anomela* | - | - | - | - | - | - | - | - | 12 | >119 |
| | *Saccharomyces cerevisiae* | - | - | - | - | 13 | 17.9 | - | - | 12 | 77 |
| Fungi | *Botrytis cinerea* | - | - | - | - | - | - | - | - | - | - |
| | *Pythium debaryanum* | - | - | - | - | - | - | - | - | - | - |

### 3.9.3 Inhibition of bacterial biofilm formation

Dr. Werner Tegge and co-workers from the Helmholtz Centre for Infection Research, Braunschweig (Germany) evaluated the *Flustra* alkaloids and their derivatives for possible inhibition of bacterial biofilm formation.

All of the 30 indole derivatives were evaluated against *S. aureus* and methicillin resistant *S. aureus* (MRSA) in three different concentrations of 1, 5, and 25 µM, respectively. Among the tested compounds, three indole derivatives showed inhibition of biofilm formation within these dosages. $N_a$-prenyl-flustrabromine (**Li-75**) was active only at a concentration of 25 µM whereas 2-*tert*-prenyl-phthaloyltryptamine (**Li-94**) showed activity at 30 µM concentration. Interestingly, 2-prenyl-phthaloyltryptamine (**Li-96**), a structural isomer to **Li-94**, is the most active among the tested compounds: It inhibited the bacterial biofilm formation at concentrations of 1, 5, and 25 µM, respectively.

# 4 Experimental Section

## 4.1 General Materials and Methods

**Chemicals and Synthesis:** All non-aqueous reactions were conducted in dried glassware under nitrogen or argon atmosphere. The chemicals were purchased in high quality from the commercial suppliers Aldrich, Acros, Fluka, ABCR, TCI, and Merck and used without further purification unless noted otherwise. All solvents were purified by standard methods and distilled prior to use. All yields refer to isolated yields of compounds after the final purification process, unless otherwise stated.

**NMR spectra** were recorded with instruments Bruker DPX-Bruker 200 (200.1 MHz for $^{1}$H NMR, $^{13}$C NMR with 50.3 MHz, T=300 K), AV II-300 (300.1 MHz for $^{1}$H NMR, $^{13}$C NMR with 75.5 MHz, T=296 K), AV III-400 (400.1 MHz for $^{1}$H NMR, $^{13}$C NMR with 100.6 MHz, T=296 K), Bruker DRX-400 (400.1 MHz for $^{1}$H NMR, $^{13}$C NMR with 100.6 MHz, T=300 K), and Bruker AV II-600 (600.1 MHz for $^{1}$H NMR; $^{13}$C NMR with 150.3 MHz). The chemical shifts $\delta$ are given in ppm and referenced to the external standard TMS or internal solvent standard. The connectivity was determined by $^{1}$H,$^{1}$H-COSY, $^{1}$H,$^{13}$C-HSQC, and $^{1}$H,$^{13}$C-HMBC experiments. Multiplicities of NMR signals are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets).

**Mass spectra** were obtained with instruments Thermofinnigan MAT95, Thermofinnigan MAT95XLT, Thermofinnigan MAT95XL, and ThermoFisher Scientific LTQ-Orbitrap Velos. For low resolution EI measurements (Thermofinnigan MAT95XL) the lower limit was set to 2000 and the high resolution was set to 10000 (10% valley definition). Depending on the method, the mass ranges were selected between 40 – 1000 amu. Measurements were performed at an ionization energy of 70 eV with the source temperature set to 180 °C. For ESI measurements (LTQ-Orbitrap Velos) the low resolution was set to 3000 and high resolution to 100000 FWHM at (*m/z* = 400 amu). Depending on method, mass ranges between 50-2000 amu were acquired.

Typical spray voltages were 2.3–2.8 kV (positive mode) and 1.7–2.5 kV (negative mode). A sample concentration of 50 µg/mL in MeOH (spiked with 0.1 mg/mL tetradecyltrimethylammonium bromide) with a flow rate of 1 µL/min was used.

For GC–MS, an Agilent 6890 gas chromatograph (analytical column: Phenomenex ZB5-MS, 30m x 0.25 mm I.D, thickness=0.25 µm) and a JMS-T100GC (GCAccuTOF, JEOL, Japan) time of flight mass spectrometer in EI mode at 70eV were used. A split injection port at 250 °C was used for sample introduction and the split ratio was set to 10:1. The helium carrier gas was set to 1.0 ml/min flow rate and the transfer line was kept at 270°C. An oven-temperature programme of starting initially at 70 °C, 3 min isothermal conditions and 10 °C/min until 300 °C was utilized for measurements

**IR spectra** were recorded with a Bruker Tensor 27 spectrometer. The wave number is given in $cm^{-1}$. The signal intensities are given in parentheses as “s” (strong), “m” (medium), “w” (weak), and “br” (broad).

**UV/Vis spectra** were measured with a Varian Cary 100 Bio UV/Vis-spectrometer. The wavelength of absorption maxima ($\lambda_{max}$) is given in nm and the extinction coefficient was given as logarithmic value in brackets.

**Melting points** were identified with a Büchi 530 melting point apparatus and are uncorrected.

**X-ray crystallography** was performed at the Institute of Inorganic and Analytical Chemistry of TU Braunschweig with an Oxford Diffraction Nova O instrument. Complete crystallographic data of the measured compounds are presented in Section 5

**Optical rotations** were measured on a Dr. Kernchen Propol Automatic Polarimeter at ambient temperature, using a 1 mL capacity cell with 1 dm path length.

**Chromatography**

**Thin layer chromatography** was performed on pre-coated plastic sheets, POLIGRAM® SIL G/$UV_{254}$ purchased from Merck (0.20 mm silica gel with fluorescent indicator $UV_{254}$). Zones were detected by fluorescence irradiation at 254 nm and/or

staining using a solution of Vaughn's reagent (9.6 g $(NH_4)_6Mo_7O_{24}\cdot 4\ H_2O$ and 0.4 g $Ce(SO_4)_2\cdot 4\ H_2O$ in 200 mL 7 M $H_2SO_4$) followed by heating.

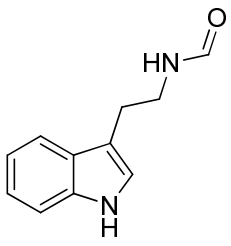
**Column chromatography/flash chromatography** was done using Geduran® Silica gel (Merck) having pore size 40-63 μm (without pressure) or 63-200 μm (with pressure) . For reversed-phase chromatography LiChroprep RP-18 (40-63 μm, 94 g, Merck) was used in a column with 3 cm diameter, which was regenerated by washing with MeOH.

**HPLC** was performed using a system consisting L-6200 intelligent pump (Merck Hitachi), a diode array detector DDT-3200 USB (Duratec) and the computer programme Clarity Data Apex. The enantiomers were separated on a chiral analytical column (Chiralcel OD, normal phase, particle size 10 μM). For reversed phase separations, analytical (LichroCART®, RP-18, particle size 5 μm) and semi-preparative columns (Hibar®, RP-18, particle size 7 μm and Phenomenex, RP-18, particle size 5 μm) were used. The HPLC grade solvents were purchased from Fisher Scientific, Honeywell, and Chromanorm

**Microwave** reactions were performed in a sealed reaction vessel ofan MLS START 1500 microwave synthesizer with an output power of 500 W.

## 4.2 Experimental Procedures

### *N*-(2-(1*H*-indol-3-yl)ethyl)formamide (125)[93]



**125**

To tryptamine (**124**, 10.2 g, 62.4 mmol, 1.0 eq.) in DCM (100 mL) was added a mixture (1:1) of $Ac_2O$ (29.6 mL, 312.0 mmol, 5.0 eq.) and $HCO_2H$ (11.9 mL, 312.0 mmol, 5.0 eq.) which were stirred at 60 °C for 1 h and allowed to cool to rt. After having added a few drops of acidic mixture, the tryptamine dissolved completely. The reaction mixture was stirred for 90 min at rt. 12 M NaOH (75 mL) was added at 0 °C and the alkaline mixture was diluted with DCM (600 mL), washed with $H_2O$ (3x 100 mL), dried over $MgSO_4$, and concentrated in vacuum. The resulting bright orange oil was further dried by heating at 70 °C under HV to give **125** (11.0 g, 58.6 mmol, 94%) as a bright orange oil.

**TLC** [silica gel, EtOAc]: $R_f$ = 0.42.

Ratio of rotamers in $CDCl_3$: 1.0:0.2.

Major rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.58 (s, br, 1H, NH), 7.97 (s, br, 1H, CHO), 7.55 (d, $^3J$ = 7.8 Hz, 1H, o-CHCHCNH), 7.31 (dd, $^4J$ = 0.9 Hz, $^3J$ = 8.0 Hz, 1H, *o*-CHC*H*CCNH), 7.20-7.06 (m, 2H, CCHC*H*C*H*CHCNH), 6.93 (d, $^3J$ = 2.3 Hz, 1H, CNHC*H*C), 5.83 (s, br, 1H, CN*H*CH), 3.57 (t, $^3J$ = 6.6 Hz, 2H, NHC$H_2$CH$_2$), 2.93 (t, $^3J$ = 6.8 Hz, 2H, NHCH$_2$C$H_2$C).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 161.3 (*C*HO), 136.3 (CH*C*NH), 127.1 ( (NHC)*C*C), 122.2 (NH*C*HC), 121.9 (*m*-CH*C*HCHCNH), 119.2 (*m*-CH*C*HCHCHCNH), 118.4 (*o*-CH*C*HCCNH), 112.1 (NHCH*C*CH$_2$), 111.3 (CH*C*HCCNH), 38.2 (CCH$_2$*C*H$_2$NHCHO), 25.0 (C*C*H$_2$CH$_2$NHCHO).

Minor rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.58 (s, br, 1H, N*H*), 7.97 (s, br, 1H, C*H*O), 7.77 (d, $^3J$ = 12.4 Hz, 1H, *o*-CHC*H*CN), 7.51 (dd, $^4J$ = 3.0 Hz, $^3J$ = 5.0 Hz, 1H, *o*-CHC*H*CCN), 7.20-7.06 (m, 2H, CCHC*H*C*H*CHCN), 6.89 (d, $^3J$ = 2.4 Hz, 1H, NHC*H*C), 5.83 (s, br,

1H, CN*H*CH), 3.53 (t, $^3J$ = 3.6 Hz, 2H, NHC$H_2$CH$_2$), 2.88 (t, $^3J$ = 6.4 Hz, 2H, NHCH$_2$C$H_2$C).

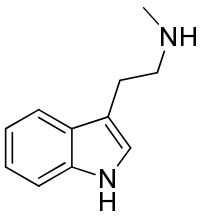
**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 164.6 (*C*HO), 136.4 (CH*C*NH), 127.2 ((NHC)*C*C), 122.1 (NH*C*HC), 121.9 (*m*-CH*C*HCHCNH), 119.2 (*m*-CH*C*HCHCHCNH), 118.2 (*o*-CH*C*HCCNH), 112.5 (NHCH*C*CH$_2$), 111.4 (CH*C*HCCNH), 39.8 (CH$_2$*C*H$_2$NHCHO), 25.1 (C*C*H$_2$CH$_2$NHCHO).

**IR** (Diamond-ATR): $\tilde{\nu}$ = 3389 cm$^{-1}$ (br, w), 3276 (br, m), 3054 (br, w), 2926 (br, w), 2872 (br, w), 1654 (s), 1516 (m), 1455 (m), 1434 (m), 1383 (m), 1339 (m), 1226 (m), 1096 (m), 1009 (w), 810 (w), 740 (br, s), 608 (m), 583 (m), 559 (m).

**UV** ($CH_2Cl_2$): $\lambda_{max}$ (log ε) = = 290 nm (3.66), 280 (3.76), 274 (3.75), 229 (4.17).

**MS** (EI, 70 eV): *m/z* (%) = 189 (2), 188 (12), 144 (8), 143 (58), 131 (14), 130 (100), 128 (8), 115 (10), 103 (15), 102 (8), 89 (6), 84 (6), 77 (21), 76 (6), 75 (5), 63 (5), 51 (10), 50 (8), 44 (7).

### 2-(1*H*-Indol-3-yl)-*N*-methylethanamine (126)[92]



**126**

$N_b$-Formyltryptamine **125** (11.0 g, 58.4 mmol, 1.0 eq.) in THF (165 mL) was stirred at rt. To this mixture DIBAL-H (17% in toluene – 261.2 mL, 267.9 mmol, 4.6 eq.) was added drop wise. The reaction mixture was stirred at rt for 24 h and afterwards added in portions to 200 g of ice and 50 mL $H_2O$ at 0 °C. 75 mL of 12 M HCl was added at 0 °C (pH 2) and the organic layer was extracted with $Et_2O$ (2x 100 mL). The aqueous layer was made strongly alkaline with NaOH (12 M, 120 mL, pH 11) and was extracted with $Et_2O$ (3x 150 mL). The resultant organic layer was washed with $H_2O$ (3x 150 mL) and all combined organic layers were dried over $MgSO_4$ and concentrated in vacuum to afford $N_b$-methyltryptamine (**126**, 8.0 g, 45.9 mmol, 79%) which solidified after drying in a desiccator over KOH.

**TLC** [silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0.1)]: $R_f$ = 0.07.

**Mp**: 88–91 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.53 (s, br, 1H, N*H*), 7.63 (dd, $^4J$ = 1.5 Hz, $^3J$ = 7.1 Hz, 1H, *o*-CHC*H*CNH), 7.33 (dd, $^4J$ = 1.2 Hz, $^3J$ = 7.0 Hz, 1H, *o*-CHC*H*CCNH), 7.20 (dd, $^4J$ = 1.4 Hz, $^3J$ = 7.0 Hz, 1H, *m*-CHC*H*CHCNH), 7.12 (dd, $^4J$ = 1.6 Hz, $^3J$ = 8.3 Hz, 1H, *m*-CHC*H*CHCCNH), 6.99 (d, $^3J$ = 1.7 Hz, 1H, NHC*H*C), 3.03-2.87 (m, 4H, NHC$H_2$C$H_2$C), 2.44 (s, 3H, NHC$H_3$), 1.89 (s, br, 1H, $CH_2$N*H*$CH_3$).

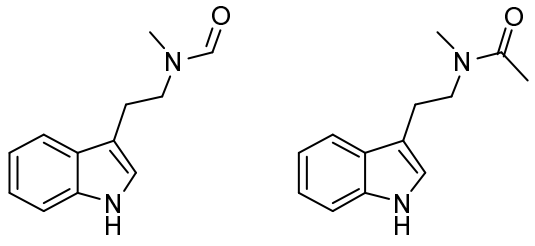
**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 136.4 (CH*C*NH), 127.4 ((NHC)*C*C), 122.0 (NH*C*HC), 121.8 (*m*-CH*C*HCHCNH), 119.1 (*m*-CH*C*HCHCHCNH), 113.7 (*o*-CH*C*HCCNH), 111.1 ($CH_2$*C*CHNHC), 52.0 ($CH_2$*C*$H_2$NHC$H_3$), 36.3 (*C*$H_3$), 25.6 (C*C*$H_2$C$H_2$NHC$H_3$).

**IR** (Diamond-ATR): $\tilde{\nu}$ = 3407 cm$^{-1}$ (w, br), 3300 (w), 3137 (w, br), 3080 (w), 2966 (w), 2930 (w), 2853 (m), 2830 (m), 2789 (m, br), 2754 (m), 2713 (w, br), 2606 (w, br), 1623 (w), 1508 (w), 1472 (w), 1452 (m), 1379 (w), 1341 (m), 1220 (m), 1160 (w), 1125 (w), 1101 (m), 1074 (w), 1011 (m), 968 (w), 894 (w), 791 (m), 769 (w), 736 (s, br), 615 (w), 587 (w), 560 (w).

**UV** ($CH_2Cl_2$): $\lambda_{max}$ (log ε) = 290 nm (3.67), 281 (3.75), 229 (4.23).

**MS** (EI, 70 eV): *m/z* (%) = 175 (8), 174 (44), 172 (14), 158 (6), 157 (6), 155 (5), 144 (28), 142 (18), 132 (10), 131 (100), 130 (84), 128 (8), 115 (6), 103 (12), 102 (8), 77 (22), 76 (6), 75 (5), 74 (5), 65 (6), 63 (5), 58 (12), 51 (12).

### *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-methylformamide (131) and *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-methylacetamide



**131** **131b**

A mixture (1:1) of $Ac_2O$ (9.0 mL, 94.5 mmol, 2.5 eq.) and $HCO_2H$ (3.6 mL, 94.5 mmol, 2.5 eq.) was stirred at 60 °C for 1 h. After cooling to rt, a solution of $N_b$-methyltryptamine **15** (6.6 g, 37.8 mmol, 1.0 eq.) in DCM (100 mL) was added drop

wise. The reaction mixture was stirred at rt for 90 min. Upon completion, the reaction mixture was added to NaOH (12 M, 110 mL, pH 11) and ice (100 g). The alkaline mixture was diluted with DCM (300 mL) and the aqueous layer was extracted twice with DCM (100 mL). The combined organic layers were washed with 2 M HCl (3x 75 mL), with $H_2O$ (3x 150 mL), dried over $MgSO_4$, filtered and concentrated in vacuum. The resulting viscous oil was dried further by stirring at 70 °C under vacuum. $Et_2O$ was added and concentrated in vacuum, affording $N_b$-formyl-$N_b$-methyltryptamine (**131**, 10.4 g, 51.7 mmol, 90%) as a brownish, semi crystalline oil which could be recrystallized using EtOAc/hexane (1:1) as needle shaped yellow crystals. Acetylated compound **131b** was also isolated as a minor product (163 mg, 0.76 mmol, 2%) as a brown oil.

Compound **131**:

**TLC** [silica gel, EtOAc]: $R_f$ = 0.3.

Ratio of rotamer in $CDCl_3$: 1.6:1.

Major rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.59 (s, br, 1H, N*H*), 7.73 (s, 1H, C*H*O), 7.53 (d, $^3J$ = 7.8 Hz, 1H, *o*-CHC*H*CNH), 7.32 (d, $^3J$ = 8.0 Hz, 1H, *o*-CHC*H*CCNH), 7.17 (dd, $^4J$ = 1.1Hz, $^3J$ = 8.0 Hz, 1H, *m*-CHC*H*CHCNH), 7.12 (dd, $^4J$ = 1.1 Hz, $^3J$ = 7.7 Hz, 1H, *m*-CHC*H*CHCCNH), 6.88 (d, $^3J$ = 2.2 Hz, 1H, NHC*H*C), 3.50 (t, $^3J$ =6.8 Hz, 2H, NC$H_2$C$H_2$C), 3.02-2.96 (m, 2H, NC$H_2$C$H_2$C), 2.91 (s, 3H, C$H_2$NC$H_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.9 (*C*HO), 136.3 (CH*C*NH), 126.7 ((NHC)*C*C), 122.5 (NH*C*HC), 121.9 (*m*-CH*C*HCHCNH), 119.3 (*m*-CH*C*HCHCCNH), 118.0 (*o*-CH*C*HCNH), 111.4 (CH$_2$*C*CHNH), 111.1 (*o*-CH*C*HCCNH), 50.0 (CH$_2$*C*H$_2$NCH$_3$), 29.6 (N*C*H$_3$), 24.2 (C*C*H$_2$CH$_2$NCH$_3$).

Minor rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.52 (s, br, 1 H, N*H*), 8.04 (s, 1 H, C*H*O), 7.65 (d, $^3J$ = 7.8 Hz, 1H, *o*-CHC*H*CNH), 7.32 (d, $^3J$ = 8.0 Hz, 1H, *o*-CHC*H*CCNH), 7.19 (dd, $^4J$ = 1.1 Hz, $^3J$ = 8.9 Hz, 1H, *m*-CHC*H*CHCNH), 7.11 (dd, $^4J$ = 1.1 Hz, $^3J$ = 7.7 Hz, 1H, *m*-CHC*H*CHCCNH), 6.97 (d, $^3J$ = 2.1 Hz,1H, NHC*H*C), 3.65 (t, $^3J$ = 7.3 Hz, 2H, NC$H_2$C$H_2$C), 3.02-2.96 (m, 2H, NC$H_2$C$H_2$C), 2.85 (s, 3H, C$H_2$NC$H_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 136.2 (CH*C*NH), 127.2 ((NHC)*C*C), 122.0 (NH*C*HC), 121.8 (*m*-CH*C*HCHCNH), 119.1 (*m*-CH*C*HCHCCNH), 118.4 (*o*-CH*C*HCNH), 112.2 ($CH_2$*C*CHNH), 111.2 (*o*-CH*C*HCCNH), 44.8 ($CH_2$*C*$H_2$N$CH_3$), 34.9 (N*C*$H_3$), 22.6 (C*C*$H_2$$CH_2$N$CH_3$).

**IR** (Diamond-ATR): $\tilde{\nu}$ = 3405 cm$^{-1}$, 3270 (w, br), 3055 (w), 2924 (w), 2862 (w), 1649 (s, br), 1488 (w), 1454 (m), 1433 (m), 1392 (m), 1339 (m), 1229 (m), 1176 (w), 1073 (m, br), 1011 (w), 739 (s), 687 (m, br), 657 (m), 621 (w), 584 (w), 560 (w).

**UV** ($CH_2Cl_2$): $\lambda_{max}$ (log ε) = 290 nm (3.68), 280 (3.77), 274 (3.76), 229 (4.22).

**MS** (EI, 70 eV): *m/z* (%) = 203 (2), 202 (14) [M$^+$], 144 (10), 143 (80), 131 (8),130 (100), 128 (5),115 (8), 103 (10), 102 (6), 77 (12), 44 (6).

Compound **131b**:

**TLC** [silica gel, EtOAc]: $R_f$ = 0.45.

Ratio of rotamer in $CDCl_3$: 1.4:1.

Major rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.53 (s, br, 1H, N*H*), 7.56 (d, $^3J$ = 7.6 Hz, 1H, *o*-CHC*H*CNH), 7.46 (d, $^3J$ = 7.2 Hz, 1H, *o*-CHC*H*CCNH), 7.26-7.00 (m, 2H, *m*-CHC*H*C*H*CNH), 6.95 (s, 1H, NHC*H*C), 3.57 (t, $^3J$ = 7.1 Hz, 2H, NC$H_2$$CH_2$C), 3.01 (t, $^3J$ = 6.7 Hz, 2H, $NCH_2$C$H_2$C), 2.98 (s, 3H, $CH_2$N(*C*$H_3$)COC$H_3$), 2.08 (s, 3H, $CH_2$N(*C*$H_3$)COC*H*$_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 170.9 (CO*C*$H_3$), 136.4 (CH*C*NH), 127.0 ((NHC)*C*C), 122.1 (NH*C*HC), 122.0 (*m*-CHCH*C*HCNH), 119.4 (*m*-CH*C*HCHCCNH), 118.5 (*o*-CH*C*HCNH), 113.0 (*o*-CH*C*HCCNH), 111.5 ($CH_2$*C*CHNH), 51.4 ($CH_2$*C*$H_2$N$CH_3$), 33.3 (N*C*$H_3$), 24.1 (C*C*$H_2$$CH_2$N$CH_3$), 21.0 ($CH_2$N(*C*$H_3$)*C*O$CH_3$).

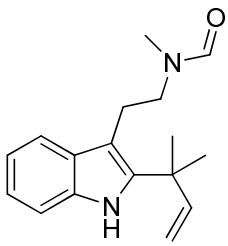
Minor rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.40 (s, br, 1H, N*H*), 7.64 (d, $^3J$ = 7.7 Hz, 1H, *o*-CHC*H*CNH), 7.34 (d, $^3J$ = 7.1 Hz, 1H, *o*-CHC*H*CCNH), 7.26-7.00 (m, 2H, *m*-CHC*H*C*H*CNH), 7.01 (s, 1H, NHC*H*C), 3.68 (t, $^3J$ = 7.1 Hz, 2H, NC$H_2$$CH_2$C), 3.01 (t,

$^{3}J$ = 6.7 Hz, 2H, $NCH_2CH_2C$), 2.90 (s, 3H, $CH_2N(CH_3)COCH_3$), 1.84 (s, 3H, $CH_2N(CH_3)COCH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 170.9 ($COCH_3$), 136.3 (CHCNH), 127.5 ((NHC)CC), 122.4 (NHCHC), 121.8 (*m*-CHCHCHCNH), 119.2 (*m*-CHCHCHCCNH), 118.6 (*o*-CHCHCNH), 111.8 ($CH_2CCHNH$), 111.1 (*o*-CHCHCCNH), 48.7 ($CH_2CH_2NCH_3$), 36.7 ($NCH_3$), 23.2 ($CCH_2CH_2NCH_3$), 22.0 ($CH_2N(CH_3)COCH_3$).

### *N*-Methyl-*N*-(2-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)-formamide (2)



**2**

To a solution of $N_b$-Formyl-$N_b$-methyltryptamine (**131**, 0.5 g, 2.5 mmol, 1.0 eq.) in THF (18 mL) and $Et_3N$ (0.4 mL, 3.0 mmol, 1.2 eq.) was added *tert*-BuOCl (**137**, 0.3 mL, 3.0 mmol, 1.2 eq.) at –78 °C. The colourless solution was stirred for 30 min at –78 °C, before a freshly prepared solution of prenyl-9-BBN (**142,** 0.5 M, 10.4 mL, 4.9 mmol, 2.0 eq.) in THF was added drop wise. It proved to be beneficial, if 1,1- dimethylallene and 9-BBN-H were allowed to react for 18 h at rt before use. After 30 min the yellow solution was allowed to warm to rt and was stirred for 1 h. Aqueous NaOH (3 M, 4 mL) and $H_2O_2$ (30%, 4 mL) were added drop wise. The mixture was stirred at rt for 1 h and diluted in $Et_2O$ (400 mL). The organic layer was washed three times with semi saturated solution of NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residual oil was washed twice with $Et_2O$ (10 mL) affording **2** (2.2 g, 8.0 mmol, 80%) as colourless solid. Further purification was possible by recrystallisation in *n*-heptane/toluene (5:1).

**TLC** [silica gel, EtOAc/petrolether (1:1)]: $R_f$ = 0.4.

**Mp**: 146-147 °C.

Ratio of rotamer in $CDCl_3$: 1.6:1.

Major Rotamer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.10 (s, br, 1H, N*H*), 8.03 (s, 1H, C*H*O), 7.44 (d, $^{3}J$ = 7.7 Hz, 1H, *o*-CHC*H*CNH), 7.31 (d, $^{3}J$ = 7.7 Hz, 1H, *o*-CHC*H*CCNH), 7.17-7.07 (m, 2H, *m*-CHC*H*C*H*CHCNH), 6.12 (dd, $^{3}J$ = 10.5, 17.4 Hz, 1H, $C(CH_3)_2CH{=}CH_2$), 5.20-

5.14 (m, 2H, $C(CH_3)_2CH=CH_2$), 3.55-3.42 (m, 2H, $CH_3NCH_2CH_2C$), 3.07-3.03 (m, 2H, $CH_3NCH_2CH_2C$), 2.97 (s, 3H, $CH_2NCH_3$), 1.52 (s, 6H, $C(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 145.8 (, $C(CH_3)_2CH=CH_2$), 140.1 ($NHCC(CH_3)_2CH$), 134.2 ((NHC)*C*C), 129.0 (CH*C*NH), 121.6 (*m*-CH*C*HCHCNH), 119.5 (*o*-CH*C*HCNH), 117.4 (*o*-CH*C*HCCNH), 111.9 ($C(CH_3)_2CH=CH_2$), 110.7 (*m*-CH*C*HCHCCNH), 106.7 ($NHCCCH_2$), 50.1 ($CH_2CH_2NCH_3$), 38.8 ($NHCC(CH_3)_2$), 29.9 ($NCH_3$), 27.6 (2C, $C(CH_3)_2CH=CH_2$) 24.9 ($CCH_2CH_2NCH_3$).

Minor rotamer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.07 (s, 1H, C*H*O), 8.00 (s, br, 1H, N*H*), 7.63 (d, $^{3}J$ = 7.5 Hz, 1H, *o*-CHC*H*CNH), 7.28 (d, $^{3}J$ = 7.3 Hz, 1H, *o*-CHC*H*CCNH), 7.17-7.07 (m, 2H, *m*-CHC*H*C*H*CHCNH), 6.13 (dd, $^{3}J$ = 10.5, 17.4 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.20-5.14 (m, 2H, $C(CH_3)_2CH=CH_2$), 3.55-3.42 (m, 2H, $CH_3NCH_2CH_2C$), 3.07-3.03 (m, 2H, $CH_3NCH_2CH_2C$), 2.95 (s, 3H, $CH_2NCH_3$), 1.56 (s, 6H, $C(CH_3)_2CH=CH_2$).

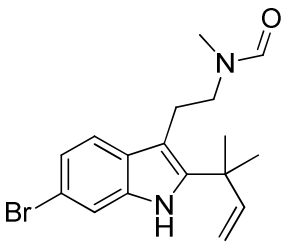
**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.3 (*C*HO), 145.7 ($C(CH_3)_2CH=CH_2$), 139.8 ($NHCC(CH_3)_2CH$), 134.1 ((NHC)*C*C), 129.5 (CH*C*NH), 121.4 (*m*-CH*C*HCHCNH), 119.3 (*o*-CH*C*HCNH), 118.1 (*o*-CH*C*HCCNH), 111.9 ($C(CH_3)_2CH=CH_2$), 110.4 (*m*-CH*C*HCHCCNH), 107.5 ($NHCCCH_2$), 45.3 ($CH_2CH_2NCH_3$), 38.9 ($NHCC(CH_3)_2$), 34.9 ($NCH_3$), 27.6 (2C, $C(CH_3)_2CH=CH_2$), 22.6 ($CCH_2CH_2NCH_3$).

**IR** (Diamond-ATR): $\tilde{\nu}$ = 3297 cm$^{-1}$ (m, br), 3051 (w), 2967 (w), 2928 (w), 2873 (w), 1651 (s), 1457 (m), 1433 (m), 1391 (m), 1359 (m), 1340 (m), 1297 (m), 1242 (m), 1167 (m), 1044 (m), 1002 (m), 913 (s), 786 (w), 758 (w), 740 (s), 723 (s), 688 (s), 657 (m), 582 (w), 532 (w).

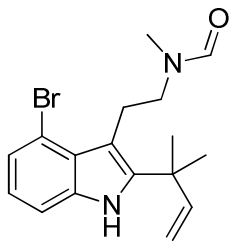
**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 290 nm (3.76), 283 (3.80), 226 (4.47), 195 (4.39), 192 (4.38).

**MS** (EI, 70 eV): *m/z* (%) = 271 (4), 270 (24) [M+], 212 (5), 211 (24), 199 (14), 198 (100), 197 (6), 196 (24), 184 (8), 183 (51), 182 (36), 181 (12), 180 (11), 170 (8), 169 (14), 168 (50), 167 (30), 166 (6), 156 (8), 154 (10), 143 (6), 130 (8), 128 (6), 115 (6), 84 (6), 82 (6), 77 (7), 67 (5), 55 (5), 44 (5).

***N*-(2-(6-Bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)-*N*-methylformamide (1) and *N*-(2-(4-bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)-*N*-methylformamide (148)**



**1**



**148**

To a stirred solution of debromoflustrabromine (**2**, 0.8 g, 2.98 mmol, 1.0 eq.) in HOAc-$HCO_2H$ (24.1 mL, 3:1) was added a solution of NBS (0.6 g, 3.1 mmol, 1.0 eq.) in HOAc-$HCO_2H$ (15 mL, 3:1). The solution was stirred at rt for 30 min, before the solution was added to a mixture of $Et_2O$ (50 mL) and ice (50 g) and again diluted with $Et_2O$ (100 mL). The organic layer was washed with $H_2O$ (3 x 50 mL) and with aqueous NaOH (1 M, 50 mL). The organic layer was washed again with $H_2O$ (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. The crude solid was washed thrice with MeOH (3 x 4 mL). Remaining solvent was removed under reduced pressure, affording flustrabromine (**1**, 0.55 g, 1.57 mmol, 53%) and 4-brominated side product **148** (0.21 g, 0.60 mmol, 20%) as a colourless solids, which were separated by column chromatography (silica gel, EtOAc/petrolether (1:1)).

6-Bromoindole **1**:

**TLC** [silica gel, EtOAc/petrolether (1:1)]: $R_f$ = 0.43.

**Mp**: 218-220 °C.

Ratio of rotamers in $CDCl_3$: 1:0.8.

Major rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.21 (s, br, 1H, indole N*H*), 7.99 (s, 1H, C*H*O), 7.49 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.46 (d, $^4J$ = 1.7 Hz, 1H, indole 7-H), 7.20 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.4 Hz, 1H, indole 5-H), 6.10 (dd, $^3J$ = 17.5, 10.4 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.21-5.15 (dd, $^3J$ = 17.5 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 5.21-5.15 (dd, $^3J$ = 10.4 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 3.53-3.38 (m,

2H, $CCH_2CH_2N(CH_3)CHO$), 3.06-2.99 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.96 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 1.52 (s, 6H, $C(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 145.5 ($C(CH_3)_2CH=CH_2$), 140.9 (indole C-2), 135.0 (indole C-7a), 128.1 (indole C-3a), 122.9 (indole C-5), 119.9 (indole C-4), 115.0 (indole C-6), 113.7 (indole C-7), 112.4 ($C(CH_3)_2CH=CH_2$), 107.1 (indole C-3), 50.2 ($CCH_2CH_2N(CH_3)CHO$), 38.9 ($NHCC(CH_3)_2CH=CH_2$), 30.1 ($CCH_2CH_2N(CH_3)CHO$), 27.6 (2C, $C(CH_3)_2CH=CH_2$), 24.9 ($CCH_2CH_2N(CH_3)CHO$).

Minor rotamer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.07 (s, br, 1H, indole N*H*), 8.00 (s, 1H, C*H*O), 7.43 (d, $^4J$ = 1.3 Hz, 1H, indole 7-H), 7.29 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.19 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.4 Hz, 1H, indole 5-H), 6.13-6.08 (dd, $^3J$ = 17.6, 10.4 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.21-5.15 (dd, $^3J$ = 17.6 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.21-5.15 (dd, $^3J$ = 10.4 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 3.53-3.38 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 3.06-2.99 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.95 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 1.55 (s, 6H, $C(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 145.5 ($C(CH_3)_2CH=CH_2$), 140.5 (indole C-2), 134.9 (indole C-7a), 128.5 (indole C-3a), 122.7 (indole C-5), 119.5 (indole C-4), 114.9 (indole C-6), 113.4 (indole C-7), 112.3 ($C(CH_3)_2CH=CH_2$), 108.0 (indole C-3), 45.5 ($CCH_2CH_2N(CH_3)CHO$), 39.0 ($NHCC(CH_3)_2CH=CH_2$), 35.1 ($CCH_2CH_2N(CH_3)CHO$), 27.6 (2C, $C(CH_3)_2CH=CH_2$), 22.6 ($CCH_2CH_2N(CH_3)CHO$).

**IR** (ATR): $\tilde{\nu}$ = 3435 cm$^{-1}$ (m, br), 3087 (w), 3054 (w), 2972 (w), 2929 (w), 2872 (w), 1653 (s, br), 1463 (m, br), 1392 (m), 1334 (w), 1222 (m), 1164 (m), 1067 (w), 1043 (w), 995 (w), 909 (m), 863 (m), 804 (m), 784 (m), 728 (m), 695 (m), 661 (m), 633 (w), 620 (w), 590 (m), 539 (w).

**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 288 nm (3.85), 232 (4.58), 200 (4.40).

**MS** (ESI): *m/z* (%) = 348 $[M]^+$ (25), 289 $[M-C_5H_9]^+$ (33), 276 $[M-C_3H_6NO]^+$ (100).

| | | |
|---|---|---|
| HRMS (ESI): | calcd. for $C_{17}H_{21}{}^{79}BrN_2O$ $[M]^+$ | 348.0837, |
| | found | 348.0838. |

4-Bromoindole **148**:

**TLC** [silica gel, EtOAc/Petrolether (1:1)]: $R_f$ = 0.58.

**Mp**: Degrades after 155 °C.

Ratio of rotamer in $CDCl_3$: 1:0.8.

Major rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.21 (s, br, 1H, indole N*H*), 8.06 (s, 1H, C*H*O), 7.44 (dd, $^4J$ = 1.3 Hz, $^3J$ = 10.7 Hz, 1H, indole 6-H), 7.29-7.23 (m, 2H, indole 5-H, indole 7-H), 6.09 (dd, $^3J$ = 10.3, 6.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.22 (dd, $^3J$ = 14.7 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 5.18 (dd, $^3J$ = 1.4 Hz, $^2J$ = 2.2 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 3.53-3.40 (m, 2H, $CCH_2CH_2$N$(CH_3)$CHO), 3.08-2.99 (m, 2H, $CCH_2CH_2$N$(CH_3)$CHO), 2.99 (s, 3H, $CCH_2CH_2$N(C$H_3$)CHO), 1.51 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 (*C*HO), 145.4 ($C(CH_3)_2CH$=$CH_2$), 140.9 (indole C-2), 135.0 (indole C-7a), 128.0 (indole C-3a), 122.7 (indole C-5), 118.7 (indole C-6), 114.9 (indole C-4), 113.7 (indole C-7), 112.1 ($C(CH_3)_2CH$=*C*$H_2$), 106.9 (indole C-3), 50.1 ($CCH_2CH_2$N$(CH_3)$CHO), 38.8 (NHC*C*$(CH_3)_2CH$=$CH_2$), 30.0 ($CCH_2CH_2$N(*C*$H_3$)CHO), 27.6 (2C, C(*C*$H_3$)$_2$CH=$CH_2$), 24.8 (C*C*$H_2CH_2$N$(CH_3)$CHO).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.09 (s, br, 1H, indole N*H*), 7.98 (s, 1H, C*H*O), 7.21-7.15 (m, 2H, indole 5-H, indole 7-H), 6.94 (dd, $^4J$ = 1.3 Hz, $^3J$ = 8.4 Hz, 1H, indole 6-H), 6.12 (dd, $^3J$ = 10.3, 6.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.19 (dd, $^3J$ = 2.6 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 5.15 (dd, $^3J$ = 3.2 Hz, $^2J$ = 2.2 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 3.53-3.40 (m, 2H, $CCH_2CH_2$N$(CH_3)$CHO), 3.08-2.99 (m, 2H, $CCH_2CH_2$N$(CH_3)$CHO), 2.99 (s, 3H, $CCH_2CH_2$N(C$H_3$)CHO), 1.54 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.9 (*C*HO), 145.5 ($C(CH_3)_2CH$=$CH_2$), 140.5 (indole C-2), 134.9 (indole C-7a), 128.4 (indole C-3a), 122.6 (indole C-5), 119.4 (indole C-6), 114.7 (indole C-4), 113.3 (indole C-7), 112.2 ($C(CH_3)_2CH$=*C*$H_2$), 107.8 (indole C-3), 45.3 ($CCH_2CH_2$N$(CH_3)$CHO), 35.0 (NHC*C*$(CH_3)_2CH$=$CH_2$), 29.7 ($CCH_2CH_2$N(*C*$H_3$)CHO), 27.5 (2C, C(*C*$H_3$)$_2$CH=$CH_2$), 22.4 (C*C*$H_2CH_2$N$(CH_3)$CHO).

**IR** (ATR): $\tilde{\nu}$ = 3295 $cm^{-1}$ (m, br), 3081 (w), 3055 (w), 2970 (w), 2930 (w), 2872 (w), 1655 (s, br), 1463 (m, br), 1390 (m), 1333 (w), 1246 (w), 1223 (w), 1160 (m), 1067 (w), 1044 (w), 997 (w), 909 (m), 862 (w), 803 (m), 728 (m), 694 (m), 659 (w), 590 (w).

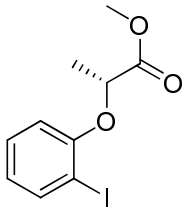
**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 289 nm (3.86), 232 (4.56), 200 (4.41).

**MS** (EI, 70 eV): *m/z* (%) = 348 $[M]^+$ (18), 289 $[M-C_5H_9]^+$ (9), 276 $[M-C_3H_6NO]^+$ (100).

**GC-HRMS** (EI): calcd. for $C_{17}H_{21}{}^{79}BrN_2O$ $[M]^+$ 348.0832,
found 348.0826.

calcd. for $C_{17}H_{21}{}^{81}BrN_2O$ $[M]^+$ 350.0811,
found 350.0809.

**(*R*)-Methyl 2-(2-iodophenoxy)propanoate (154)**[117]



**154**

A solution of diisopropylazodicarboxylate (DIAD, 16.83 mL, 0.08 mmol, 1.51 eq.) in toluene (35 mL) was added drop wise to a solution of $Ph_3P$ (21.28 g, 0.08 mmol, 1.51 eq.), (*S*)-methyllactate (8.07 mL, 0.08 mmol, 1.51 eq.), and 2-iodophenol (**153**, 11.94 g, 0.053 mmol, 1.0 eq.) in THF (240 mL) at rt. The reaction mixture was stirred at rt for 4.5 h and concentrated in vacuum. The resulting yellow residue was purified by chromatography (silica gel, Petrolether/EtOAc (15:1 to 1:1) to obtain the title compound **154** (13.2 g, 0.043 mmol, 81%) as a yellow oil.

**TLC** [silica gel, EtOAc/Petrolether (4:1)]: $R_f$ = 0.62.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.79 (dd, $^4J$ = 1.6 Hz, $^3J$ = 7.8 Hz, 1H, 3-H), 7.27-7.22 (m, 1H, 5-H), 6.74 (dd, $^4J$ = 1.4 Hz, $^3J$ = 7.5 Hz, 1H, 4-H), 6.71 (dd, $^4J$ = 1.4 Hz, $^3J$ = 8.0 Hz, 1H, 6-H), 4.76 (q, $^3J$ = 6.8 Hz, 1H, OC*H*($CH_3$)$COOCH_3$), 3.76 (s, 3H, OCH($CH_3$)COOC*H*$_3$), 1.70 (d, $^3J$ = 6.8 Hz, 3H, OCH(C*H*$_3$)$COOCH_3$).

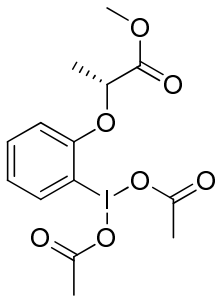
**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 172.1 (OCH($CH_3$)*C*$OOCH_3$), 156.6 (C-1), 139.8 (C-3), 129.3 (C-5), 123.5 (C-4), 113.4 (C-6), 87.3 (C-2), 74.1 (O*C*H($CH_3$)$COOCH_3$), 52.3 (OCH($CH_3$)COO*C*$H_3$), 18.6 (OCH(*C*$H_3$)$COOCH_3$).

**IR** (ATR): $\tilde{\nu}$ = 3062 $cm^{-1}$ (w), 2992 (w), 2951 (w), 1754 (s), 1736 (s), 1580 (w), 1469 (s), 1438 (m), 1375 (w), 1277 (m), 1240 (m), 1203 (s), 1133 (s), 1094 (s), 1050 (m), 1017 (s), 973 (m), 933 (w), 844 (w), 806 (w), 745 (s), 648 (m), 599 (w).

**UV** (DMSO): $\lambda_{max}$ (log ε) = 333 nm (1.65), 285 (3.40), 278 (3.44), 254 (3.18), 252 (3.16).

**GCMS** (EI, 70 eV): *m/z* (%) = 307 (8), 306 (61), 248 (8), 247 (83), 221 (8), 220 (91), 219 (5), 203 (26), 191 (6), 180 (13), 179 (100), 148 (9), 146 (7), 121 (18), 120 (40), 105 (7), 104 (9), 94 (9), 93 (21), 92 (22), 91 (10), 87 (5), 77 (13), 76 (32), 65 (25), 64 (18), 63 (16), 59 (12), 55 (12), 50 (14), 44 (14).

### (*R*)-Methyl-2-(2-(diacetoxyiodo)phenoxy)propanoate (155)[118]



**155**

The mixture of $Ac_2O$ (60 mL, 634.7 mmol, 63.47 eq.) and $H_2O_2$ (30%, 14 mL, 137.04 mmol, 13.704 eq.) was stirred at 40 °C for 16 h. To the in situ generated Acetoxyperacid, 2-iodophenoxypropanoate methyl ester (**154**, 3.06 g, 10.0 mmol, 1.0 eq.) was added drop wise and stirred further at 45 °C for 24 h. The reaction mixture was diluted with DCM (200 mL) and $H_2O$ (100 mL). The aqueous layer was extracted with DCM (2 x 100 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude reaction mixture was repeatedly washed with pentane (8 x 5 mL) to obtain the title compound **155** (2.26 g, 5.33 mmol, 53%) as an amorphous white solid. (The reaction was performed with caution as the in-situ generated Acetoxyperacids are explosive).

**Mp**: 124-126 °C [132 °C].

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.15 (dd, $^4J$ = 1.6 Hz, $^3J$ = 7.9 Hz, 1H, 3-H), 7.53 (ddd, $^4J$ = 1.6 Hz, $^3J$ = 8.4, 7.4 Hz, 1H, 5-H), 7.07 (ddd, $^4J$ = 1.3 Hz, $^3J$ = 7.8, 7.5 Hz, 1H, 4-H), 7.00 (dd, $^4J$ = 1.2 Hz, $^3J$ = 8.4 Hz, 1H, 6-H), 4.90 (q, $^3J$ = 6.8 Hz, 1H, OC*H*($CH_3$)$COOCH_3$), 3.77 (s, 3H, OCH($CH_3$)$COOCH_3$), 1.98 (s, 6H, I($OCOCH_3$)$_2$), 1.70 (d, $^3J$ = 6.8 Hz, 3H, OCH($CH_3$)$COOCH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 176.6 (2C, I($OCOCH_3$)$_2$), 171.2 (OCH($CH_3$)$COOCH_3$), 154.6 (C-1), 137.8 (C-3), 134.2 (C-5), 123.6 (C-4), 114.2 (C-

2), 113.3 (C-6), 74.4 (O*C*H($CH_3$)COO$CH_3$), 52.5 (OCH($CH_3$)COO*C*$H_3$), 20.3 (2C, I(OCO*C*$H_3$)$_2$), 18.3 (OCH(*C*$H_3$)COO$CH_3$).

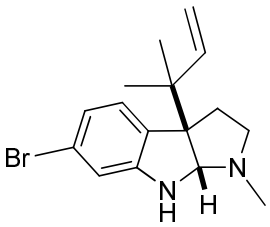
**IR** (ATR): $\tilde{\nu}$ = 3090 cm$^{-1}$ (w), 3020 (w), 2987 (w), 2957 (w), 1740 (s), 1647 (s), 1587 (m), 1570 (w), 1474 (m), 1444 (m), 1364 (m), 1270 (s, br), 1244 (s, br), 1165 (w), 1134 (m), 1090 (s), 1052 (m), 1011 (m), 975 (m), 923 (m), 842 (m), 802 (m), 765 (s), 612 (m), 566 (w).

**UV** (MeOH): $\lambda_{max}$ (log ε) = 284 nm (3.59), 204 (4.42).

**MS** (ESI): *m/z* (%) = 361 (8), 347 (11), 345 (100), 339 (4), 329 (32), 325 (10), 323 (94), 301 (6).

**HRMS** (ESI): calcd. for $C_{10}H_{11}INaO_5$ [M+H+Na-($C_4H_7O_2$)]$^+$ 360.9549,
found 360.9543.

**6-Bromo-1-methyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo [2,3-*b*]indole (*rac*-dihydroflustramine C, 7)**




**7**

At rt, DIBAL-H (20% in toluene, 0.48 mL, 0.57 mmol, 1.8 eq.) was added drop wise to a solution of *rac*-flustramine C[116] (**5**, 100 mg, 0.31 mmol, 1.0 eq.) in THF (10 mL). The reaction mixture was stirred at rt for 26 h and added drop wise to ice water (250 mL). The reaction mixture was diluted with $Et_2O$ (75 mL) and made strongly alkaline with aqueous NaOH (12 M 35 mL). The aqueous layer was extracted with $Et_2O$ (3 x 50 mL), washed with $H_2O$ (3 x 50 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum to afford *rac*-dihydroflustramine C (**7**, 94 mg, 0.293 mmol, 93%) as a yellow oil.

**TLC** [silica gel, EtOAc/petrolether (1:1)]: $R_f$ = 0.2

**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ = 6.95 (d, $^3J$ = 7.0 Hz, 1H, 4-H), 6.77 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.0 Hz, 1H, 5-H), 6.67 (d, $^4J$ = 1.7 Hz, 1H, 7-H), 5.96 (dd, $^3J$ = 17.4 Hz, 10.8 Hz, 1H, C($CH_3$)$_2$C*H*=$CH_2$), 5.07 (dd, $^3J$ = 10.8 Hz, $^2J$ = 1.2 Hz, 1H, C($CH_3$)$_2$CH=C$H_2$-$H_Z$), 5.01 (dd, $^3J$ = 17.4 Hz, $^2J$ = 1.2 Hz, 1H, C($CH_3$)$_2$CH=C$H_2$-$H_E$), 4.39 (s, 1H, 8a-H), 4.26 (s, br, 1H, 8-H), 2.59 (ddd, $^3J$ = 6.9, 4.2, 2.1Hz, $^2J$ = 11.7 Hz, 1H,

$CH_2CH_2N(CH_3)$), 2.52 (ddd, $^3J$ = 6.1, 4.9, 3.7 Hz, $^2J$ = 1.2 Hz, 1H, $CH_2CH_2N(CH_3)$), 2.37 (s, 3H, $NCH_3$), 2.27 (ddd, , $^3J$ = 9.7, 7.1, 2.0 Hz, $^2J$ = 12.2 Hz, 1H, $CH_2CH_2N(CH_3)$), 1.79 (ddd, $^3J$ = 5.5, 5.0 Hz, $^2J$ = 12.0 Hz, 1H, $CH_2CH_2N(CH_3)$), 1.03 (s, 3H, $C(CH_3)_2CH=CH_2$), 0.99 (s, 3H, $C(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (75.5 MHz, $CDCl_3$): $\delta$ = 152.0 (C-7a), 144.6 ($C(CH_3)_2CH=CH_2$), 132.6 (C-3b), 126.2 (C-4), 121.2 (C-6), 120.6 (C-5), 113.1 ($C(CH_3)_2CH=CH_2$), 111.5 (C-7), 84.4 (C-8a), 63.9 (C-3a), 53.0 (C-2), 41.2 ($HNCHC(CH_3)_2$), 36.8 ($NCH_3$), 34.7 (C-3), 23.1 ($C(CH_3)_2CH=CH_2$), 22.3 ($C(CH_3)_2CH=CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3413 cm$^{-1}$ (w, br), 3260 (w, br), 3081 (w), 3033 (w), 2965 (m), 2935 (m), 2870 (w), 2843 (w), 2790 (w), 1595 (s), 1481 (s), 1446 (s), 1414 (m), 1380 (w), 1365 (m), 1349 (m), 1310 (m), 1249 (m, br), 1155 (m), 1120 (m), 1097 (w), 1072 (m), 1048 (m), 1004 (s), 942 (w), 910 (s), 886 (m), 834 (m), 789 (s), 687 (m), 605 (m).

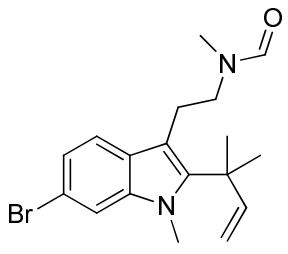
**UV** (MeOH): $\lambda_{max}$ (log ε) = 356 nm (2.17), 350 (2.20), 308 (3.58), 251 (3.75), 228 (3.90).

**MS** (EI, 70 eV): *m/z* (%) = 320 $[M]^+$ (22), 249 $[M-C_5H_9]^+$ (100), 207 (32), 172 (43).

**GC-HRMS** (EI): calcd. for $C_{16}H_{21}{}^{79}N_2Br$ $[M]^+$ 320.0883,
found 320.0883

calcd. for $C_{16}H_{21}{}^{81}N_2Br$ $[M]^+$ 322.0862,
found 322.0864.

### *N*-(2-(6-bromo-1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)-*N*-methylformamide (163)




**163**

NaH (60% suspension in mineral oil, 232 mg, 5.80 mmol, 1.5 eq.) was washed with pentane (2 mL) and dried in HV. At 0 °C, a solution of flustrabromine (**1**, 1.35 g, 3.87 mmol, 1.0 eq.) in DMF (32 mL) was added drop wise. After 1 h at 0 °C, a solution of MeI (610 mg, 4.25 mmol, 1.1 eq.) in DMF (10 mL) was added drop wise, and the reaction mixture was stirred at rt for 2 h. $H_2O$ (50 mL) was added cautiously and the reaction mixture was extracted

with TBME (3 x 100 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL) and brine (1 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc/petrolether (1:1)) to obtain the title compound **163** (1.01 g, 2.77 mmol, 72%) as a yellow oil.

**TLC** [silica gel, EtOAc/petrolether (1:1)]: $R_f$ = 0.42.

Ratio of rotamers in $CDCl_3$: 1:0.8.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.98 (s, 1H, C*H*O), 7.39 (d, $^4J$ = 1.6 Hz, 1H, indole 7-H), 7.31 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.22 (dd, $^4J$ = 1.7 Hz, 1H, $^3J$ = 3.0 Hz, 1H, indole 5-H), 6.15 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.12 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 4.97 (t, $^2J$ = 0.7 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 3.68 (s, 3H, CN(C$H_3$)C), 3.42-3.38 (m, 2H, $CCH_2CH_2$N($CH_3$)CHO), 3.20-3.15 (m, 2H, $CCH_2CH_2$N($CH_3$)CHO), 2.96 (s, 3H, $CCH_2CH_2$N(C$H_3$)CHO), 1.61 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 147.0 ($C(CH_3)_2CH$=$CH_2$), 141.4 (indole C-2), 138.6 (indole C-7a), 127.0 (indole C-3a), 122.4 (indole C-5), 118.7 (indole C-4), 115.5 (indole C-6), 112.4 ($C(CH_3)_2CH$=$CH_2$), 112.0 (indole C-7), 107.9 (indole C-3), 51.3 ($CCH_2CH_2$N($CH_3$)CHO), 40.7 (CN($CH_3$)C*C*($CH_3$)$_2$CH=$CH_2$), 33.4 (CHCN(*C*H$_3$)CC($CH_3$)$_2$), 30.1 ($CCH_2CH_2$N(*C*H$_3$)CHO), 29.4 (2C, C(*C*H$_3$)$_2$CH=$CH_2$) 25.4 (C*C*$H_2CH_2$N($CH_3$)CHO).

Minor rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.05 (s, 1H, C*H*O), 7.50 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.37 (d, $^4J$ = 1.7 Hz, 1H, indole 7-H), 7.19 (dd, $^4J$ = 1.7 Hz, 1H, $^3J$ = 3.0 Hz, 1H, indole 5-H), 6.16 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.10 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 4.93 (t, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 3.67 (s, 3H, CN(C$H_3$)C), 3.48-3.44 (m, 2H, $CCH_2CH_2$N($CH_3$)CHO), 3.20-3.15 (m, 2H, $CCH_2CH_2$N($CH_3$)CHO), 2.93 (s, 3H, $CCH_2CH_2$N(C$H_3$)CHO), 1.65 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 (*C*HO), 147.3 ($C(CH_3)_2CH=CH_2$), 141.2 (indole C-2), 138.5 (indole C-7a), 127.5 (indole C-3a), 122.3 (indole C-5), 119.3 (indole C-4), 115.3 (indole C-6), 112.2 ($C(CH_3)_2CH=CH_2$), 111.7 (indole C-7), 108.8 (indole C-3), 46.6 ($CCH_2CH_2N(CH_3)CHO$), 40.8 ($CN(CH_3)CC(CH_3)_2CH=CH_2$), 35.1 ($CCH_2CH_2N(CH_3)CHO$), 33.3 ($CHCN(CH_3)CC(CH_3)_2$), 29.4 (2C, $C(CH_3)_2CH=CH_2$), 23.0 ($CCH_2CH_2N(CH_3)CHO$).

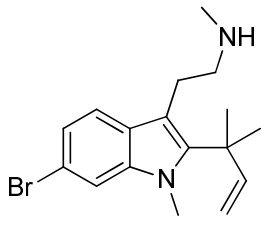
**IR** (ATR): $\tilde{\nu}$ = 3078 cm$^{-1}$ (w), 2969 (w), 2927 (w), 2871 (w), 1668 (s), 1601 (w), 1473 (m), 1387 (m), 1355 (w), 1331 (w), 1298 (w), 1229 (m), 1177 (w), 1138 (w), 1080 (m), 995 (w), 915 (m), 845 (m), 802 (m),.745 (m), 655 (w),.593 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 301 nm (3.89), 294 (3.90), 241 (4.39), 231 (3.89).

**MS** (EI, 70 eV): *m/z* (%) = 365 $[M+H]^+$ (4), 364 $[M]^+$ (19), 363 $[M+H]^+$ (4), 362 $[M]^+$ (21), 293 (21), 292 (98), 291 (19), 290 (100), 278 (7), 277 (50), 276 (25), 275 (50), 274 (21), 264 (6), 263 (11), 262 (24), 261 (16), 260 (25), 259 (6), 258 (6), 249 (5), 248 (5), 247 (10), 246 (8), 245 (7), 223 (6), 221 (8), 211 (23), 210 (10), 209 (16), 208 (5), 197 (9), 196 (58),.195 (65),.194 (40),.193 (7),.183 (7),.182 (28),.181 (93),.180 (46),.179 (9),.178 (7),.169 (14),.168 (32),.167 (28),.166 (14),.165 (5),.156 (13),.155 (8),.154 (7),.128 (9),.127 (8),.115 (14),.72 (32).

**GC-HRMS** (EI): calcd. for $C_{18}H_{23}BrN_2O$ $[M]^+$ 362.0988,
found 362.0983.

**2-(6-Bromo-1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)-*N*-methylethanamine (10)**



**10**

To a solution of $N_a$-methylflustrabromine (**163**, 881 mg, 2.42 mmol, 1.0 eq.) in EtOH (100 mL) was added aqueous NaOH (32%, 12 mL). The reaction mixture was refluxed for 60 h and cooled to rt. $H_2O$ (50 mL) was added and the reaction mixture was extracted with EtOAc (3 x 100 mL), washed with $H_2O$ (4 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and filtered. The solvent was removed under reduced pressure affording the pure title compound **10** (779 mg, 2.32 mmol, 96%) as a slight yellow oil.

**TLC** [silica gel, $CHCl_3$/MeOH (9:1)]: $R_f$ = 0.07.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.44 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.36 (d, $^4J$ = 1.6 Hz, 1H, indole 7-H), 7.17 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.4 Hz, 1H, indole 5-H), 6.14 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.09 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 4.93 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 3.65 (s, 3H, CN(C$H_3$)C), 3.18-3.14 (m, 2H, CC$H_2$$CH_2NHCH_3$), 2.83-2.79 (m, 2H, $CCH_2$C$H_2$$NHCH_3$), 2.47 (s, 3H, $CCH_2CH_2NHCH_3$), 1.89 (s, br, 1H, $CCH_2CH_2$N$H$$CH_3$), 1.62 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 147.5 ($C(CH_3)_2$*C*H=$CH_2$), 140.9 (indole C-2), 138.5 (indole C-7a), 127.7 (indole C-3a), 122.0 (indole C-5), 119.5 (indole C-4), 115.5 (indole C-6), 112.1 ($C(CH_3)_2CH$=*C*$H_2$), 111.6 (indole C-7), 110.0 (indole C-3), 54.1 ($CCH_2$*C*$H_2NHCH_3$), 40.8 (N($CH_3$)C*C*($CH_3$)$_2$CH=$CH_2$), 36.4 ($CCH_2CH_2NH$*C*$H_3$), 33.3 (CHCN(*C*$H_3$)CC), 29.5 (2C, C(*C*$H_3$)$_2$CH=$CH_2$), 25.7 (C*C*$H_2CH_2NHCH_3$).

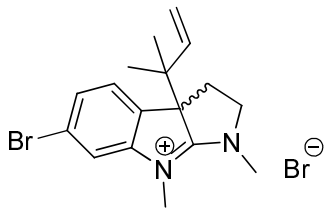
**IR** (ATR): $\tilde{\nu}$ = 3318 cm$^{-1}$ (w), 3078 (w), 2968 (m), 2933 (m), 2879 (m), 2790 (w), 1633 (w), 1600 (w), 1472 (s), 1448 (m), 1383 (w), 1353 (m), 1330 (m), 1295 (w), 1229 (m), 1137 (m), 1110 (m), 1085 (w), 1058 (m), 992 (m), 914 (m), 846 (), 800 (s), 750 (s), 686 (w), 563 (w), 592 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 301 nm (3.84), 294 (3.85), 241 (4.35), 231 (3.89).

**MS** (EI, 70 eV): *m/z* (%) = 337 $[M+H]^+$ (2), 336 $[M]^+$ (5), 335 $[M+H]^+$ (2), 334 $[M]^+$ (6), 294 (26), 293 (98), 292 (76), 291 (100), 290 (62), 279 (14), 278 (65), 277 (62), 276 (75), 275 (58), 274 (21), 266 (9), 265 (14), 264 (22), 263 (16), 262 (21), 261 (6), 249 (8), 248 (7), 247 (13), 236 (8), 224 (9), 222 (10), 212 (7), 211 (13), 210 (9), 209 (7), 197 (16),196 (53), 195 (48), 194 (24), 183 (9), 182 (39), 181 (53), 180 (27), 186 (6), 169 (9), 168 (18), 167 (16), 166 (8), 154 (8), 155 (6), 154 (7), 143 (7), 128 (7), 127 (6), 115 (8), 102 (5).

| | | |
|---|---|---|
| **GC-HRMS** (EI): | calcd. for $C_{17}H_{23}BrN_2$ $[M]^+$ | 334.1039, |
| | found | 334.1040. |

**6-Bromo-1,8-dimethyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indol-8-ium bromide (12)**



**12**

To a solution of $N_a$-methyldeformylflustrabromine (**10**, 715 mg, 2.13 mmol, 1.0 eq.) in THF (20 mL) at 0 °C was added NBS (426 mg, 2.345 mmol, 1.1 eq.). After 1 h, the precipitate was washed with EtOAc (3 x 5 mL) and dried in vacuum to afford compound **12** (549 mg, 1.33 mmol, 62%) as a colourless amorphous solid.

**Mp**: 165-166 °C.

**$^1$H NMR** (400 MHz, $D_2O$): $\delta$ = 7.40-7.37 (m, 2H, *5*-H, 7-H), 7.28 (d, $^3J$ = 8.4 Hz, 1H, 4-H), 5.93 (dd, $^3J$ = 17.4, 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.17 (dd, $^3J$ = 10.8 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.12 (dd, $^3J$ = 17.4 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.46 (ddd, $^3J$ = 9.5, 6.3 Hz, $^2J$ = 11.9 Hz, 1H, =$CN(CH_3)CH_2CH_2C$), 4.00 (dd, $^3J$ = 11.7, 10.0 Hz, 1H, =$CN(CH_3)CH_2CH_2C$), 3.67 (s, 3H, $CN^+(CH_3)$=$CN(CH_3)CH_2CH_2C$), 3.55 (s, 3H, $CN^+(CH_3)$=$CN(CH_3)CH_2CH_2C$), 2.70 (dd, $^3J$ = 5.9 Hz, $^2J$ = 13.5, 1H, $N(CH_3)CH_2CH_2C$), 2.43 (td, $^3J$ = 9.8 Hz, $^2J$ = 13.4 Hz, 1H, $N(CH_3)CH_2CH_2C$), 1.09 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.93 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $D_2O$): $\delta$ = 181.1 (C-8a), 152.7 (C-7a), 144.2 ($C(CH_3)_2CH$=$CH_2$), 133.3 (C-3b), 129.5 (C-5), 128.9 (C-4), 124.9 (C-6), 116.5 (C-7), 118.4 ($C(CH_3)_2CH$=$CH_2$), 71.5 (C-3a), 67.9 (C-2), 48.6 ($N^+(CH_3)$=$CCC(CH_3)_2CH$=$CH_2$), 37.4 ($N^+(CH_3)$=$CN(CH_3)CH_2CH_2C$), 33.6 ($N^+(CH_3)$=$CN(CH_3)CH_2CH_2C$), 29.5 ($CCH_2CH_2N(CH_3)C$), 25.8 ($C(CH_3)_2CH$=$CH_2$), 24.7 ($C(CH_3)_2CH$=$CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 2966 cm$^{-1}$ (w), 2922 (w), 2852 (w), 1698 (s), 1603 (m), 1493 (m), 1451 (w), 1413 (m), 1395 (m), 1372 (w), 1318 (w), 1288 (w), 1254 (w), 1153 (w), 1108 (m), 1060 (w), 1013 (w), 981 (w), 928 (m), 878 (w), 836 (s), 765 (w), 734 (w), 712 (w), 662 (w), 609 (m), 585 (w), 563 (w), 540 (w).

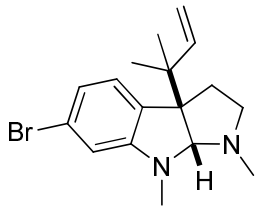
**UV** (DMSO): $\lambda_{max}$ (log ε) = 283 nm (3.82), 253 (3.60).

**MS** (ESI): *m/z* (%) = 336 $[M+H]^+$ (18), 335 $[M]^+$ (96), 334 $[M+H]^+$ (17), 333 $[M]^+$ (100), 267 (6), 266 (49), 265 (12), 264 (49), 263 (12), 254 (10).

**HRMS** (ESI): calcd. for $C_{17}H_{22}BrN_2^+$ $[M]^+$ 333.0961,

found 333.0965.

**(3a,8a)-6-Bromo-1,8-dimethyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (15)**



**15**

Indole derivative **12** (459 mg, 1.11 mmol, 1.0 eq.) in MeOH (10 mL) was added to $NaBH_4$ (30 mg, 0.78 mmol, 0.7 eq.) under Ar, at rt. The reaction mixture was stirred further for 24 h at rt and diluted cautiously with $H_2O$ (10 mL), followed by 2 N NaOH (50 mL). The aqueous phase was extracted with TBME (3 x 100 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL), brine (50 mL), dried over $Na_2SO_4$; filtered, and concentrated in vacuum. The crude residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0 to 9:1:0.1) to obtain the title compound **15** (204 mg, 0.61 mmol, 55%) as a colorless oil.

**TLC** [silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0.1)]: $R_f$ = 0.91.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 6.90 (d, $^3J$ = 7.9 Hz, 1H, 4-H), 6.70 (d, $^4J$ = 1.8 Hz, $^3J$ = 7.9 Hz, 1H, 5-H), 6.46 (d, $^4J$ = 1.8 Hz, 1H, 7-H), 5.91 (dd, $^3J$ = 17.4, 10.8 Hz, 1H, ($C(CH_3)_2CH$=$CH_2$), 5.06 (dd, $^3J$ = 10.8 Hz, $^2J$ = 1.3 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 4.99 (dd, $^3J$ = 17.4 Hz, $^2J$ = 1.4 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.20 (s, 1H, 8a-H), 2.92 (s, 3H, $CN(CH_3)CHN(CH_3)CH_2$), 2.66 (ddd, $^3J$ = 6.6, 2.9 Hz, $^2J$ = 9.4, 1H, $CHN(CH_3)CH_2CH_2C$), 2.47-2.41 (m, 1H, $CHN(CH_3)CH_2CH_2C$), 2.43 (s, 3H, $CN(CH_3)CHN(CH_3)CH_2$), 2.24 (ddd, $^3J$ = 9.4, 6.7 Hz, $^2J$ = 11.9, 1H, $CHN(CH_3)CH_2CH_2C$), 1.76 (ddd, $^3J$ = 5.5, 2.9 Hz, $^2J$ = 11.9 Hz, 1H, $CHN(CH_3)CH_2CH_2C$), 1.00 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.94 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 154.2 (C-7a), 144.8 ($C(CH_3)_2CH$=$CH_2$), 132.3 (C-3b), 125.7 (C-4), 121.8 (C-6), 119.2 (C-5), 113.1 ($C(CH_3)_2CH$=$CH_2$), 108.9 (C-7), 91.4 (C-8a), 63.6 (C-3a), 53.4 (C-2), 41.0 ($NCHC(CH_3)_2CH$=$CH_2$), 37.7 ($CN(CH_3)CHN(CH_3)CH_2$), 35.1 ($CN(CH_3)CHN(CH_3)CH_2$), 34.3 (C-3), 23.4 ($C(CH_3)_2CH$=$CH_2$), 22.4 ($C(CH_3)_2CH$=$CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3080 cm$^{-1}$ (w), 2964 (m), 2930 (m), 2870 (w), 2792 (w), 1724 (w), 1635 (s), 1593 (s), 1493 (s), 1443 (m), 1410 (m), 1367 (w), 1346 (w), 1315 (w), 1257 (m),

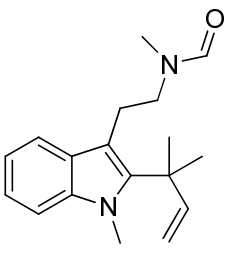
1207 (w), 1158 (m), 1116 (m), 1069 (w), 1044 (m), 974 (m), 914 (s), 823 (s), 798 (m), 781 (m), 753 (w), 692 (w), 661 (w), 623 (w), 609 (m), 577 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 319 nm (3.63), 264 (3.91), 236 (3.75), 231 (3.74).

**MS** (ESI): *m/z* (%) = 357 $[M+Na]^+$ (7), 336 $[M+H]^+$ (19), 335 $[M]^+$ (100), 334 (18), 333 (99), 307 (9), 306 (51), 305 (9), 304 (56), 294 (8), 292 (8), 255 (12), 238 (35), 236 (35), 226 (5), 224 (5), 186 (5).

**HRMS** (ESI): calcd. for $C_{17}H_{24}BrN_2^+$ $[M+H]^+$ 335.1117,
found 335.1122.

### *N*-Methyl-*N*-(2-(1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl) formamide (164)



**164**

NaH (60% suspension in mineral oil, 222 mg, 5.552 mmol, 1.5 eq.) was washed with pentane (5 mL) and dried in HV. At 0 °C, a solution of debromoflustrabromine (**2**, 1.0 g, 3.701 mmol, 1.0 eq.) in DMF (30 mL) was added. After 30 min at 0 °C, a solution of MeI (580 mg, 4.072 mmol, 1.1 eq.) in DMF (10 mL) was added drop wise, and the reaction mixture was stirred at rt for 45 min. $H_2O$ (40 mL) was added cautiously and the reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL) and brine (1 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum to afford the pure title compound **164** (1.04 g, 3.66 mmol, 99%) as a yellow oil.

Ratio of rotamers in $CDCl_3$: 1.7:1.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.02 (s, 1H, C*H*O), 7.47 (d, $^3J$ = 7.0 Hz, 1H, indole 4-H), 7.26-7:18 (m, 2H, indole 6-H, indole 7-H), 7.14-7.01 (m, 1H, indole 5-H), 6.17 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.10 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.99 (t, $^3J$ = 1.0 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 3.72 (s, 3H, $CN(CH_3)C$), 3.45-3.41 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 3.24-3.19 (m, 2H,

CC*H*$_2$CH$_2$N(CH$_3$)CHO), 2.98 (s, 3H, CCH$_2$CH$_2$N(C*H*$_3$)CHO), 1.62 (s, 6H, C(C*H*$_3$)$_2$CH=CH$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ = 162.5 (*C*HO), 147.4 (C(CH$_3$)$_2$*C*H=CH$_2$), 140.7 (indole C-2), 137.7 (indole C-7a), 128.1 (indole C-3a), 121.8 (indole C-6), 119.3 (indole C-5), 117.4 (indole C-4), 112.1 (C(CH$_3$)$_2$CH=*C*H$_2$), 108.9 (indole C-7), 107.6 (indole C-3), 51.3 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 40.7 (CN(CH$_3$)C*C*(CH$_3$)$_2$CH), 33.2 (CHCN(*C*H$_3$)C), 30.1 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 29.4 (2C, C(*C*H$_3$)$_2$CH=CH$_2$) 25.5 (C*C*H$_2$CH$_2$N(CH$_3$)CHO).

Minor rotamer:

**$^{1}$H NMR** (400 MHz, CDCl$_3$): $\delta$ = 8.06 (s, 1H, C*H*O), 7.64 (d, $^{3}J$ = 7.0 Hz, 1H, indole 4-H), 7.26-7.18 (m, 2H, indole 6-H, indole 7-H), 7.14-7.01 (m, 1H, indole 5-H), 6.18 (dd, $^{3}J$ = 17.5, 10.6 Hz, 1H, C(CH$_3$)$_2$C*H*=CH$_2$), 5.09 (dd, $^{3}J$ = 10.6 Hz, $^{2}J$ = 1.0 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_Z$), 4.94 (t, $^{3}J$ = 1.0 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_E$), 3.71 (s, 3H, CN(C*H*$_3$)C), 3.52-3.48 (m, 2H, CCH$_2$C*H*$_2$N(CH$_3$)CHO), 3.24-3.19 (m, 2H, CC*H*$_2$CH$_2$N(CH$_3$)CHO), 2.96 (s, 3H, CCH$_2$CH$_2$N(C*H*$_3$)CHO), 1.66 (s, 6H, C(C*H*$_3$)$_2$CH=CH$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ = 162.4 (*C*HO), 147.7 (C(CH$_3$)$_2$*C*H=CH$_2$), 140.6 (indole C-2), 137.6 (indole C-7a), 128.5 (indole C-3a), 121.6 (indole C-6), 119.1 (indole C-5), 118.0 (indole C-4), 111.9 (C(CH$_3$)$_2$CH=*C*H$_2$), 108.6 (indole C-7), 108.4 (indole C-3), 46.6 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 40.8 (CN(CH$_3$)C*C*(CH$_3$)$_2$CH), 35.1 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 33.2 (CHCN(*C*H$_3$)C), 29.5 (2C, C(*C*H$_3$)$_2$CH=CH$_2$), 23.1 (C*C*H$_2$CH$_2$N(CH$_3$)CHO).

**IR** (ATR): $\tilde{\nu}$ = 3050 cm$^{-1}$ (w), 2970 (w), 2930 (w), 2873 (w), 1669 (s), 1474 (m), 1383 (m), 1355 (m), 1320 (w), 1232 (w), 1177 (w), 1148 (w), 1081 (m), 1015 (w), 995 (w), 913 (m), 741 (s), 562 (w).

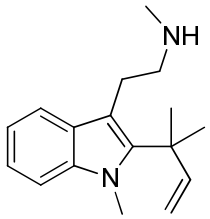
**UV** (CHCl$_3$): $\lambda_{max}$ (log ε) = 290 nm (3.84), 240 (4.09).

**MS** (EI, 70 eV): *m/z* (%) = 284 [M]$^+$ (20), 212 [M-C$_3$H$_6$NO]$^+$ (100), 198 [M-C$_4$H$_8$NO]$^+$ (10), 182 (55).

**GC-HRMS** (EI): calcd. for C$_{18}$H$_{24}$N$_2$O [M]$^+$ 284.1883,

found 284.1859.

### *N*-Methyl-2-(1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine (11)



**11**

To a solution of $N_a$-methyldebromoflustrabromine (**164**, 600 mg, 2.11 mmol, 1.0 eq.) in EtOH (80 mL) was added aqueous NaOH (32%, 8 mL). The reaction mixture was refluxed for 48 h and cooled to rt. $H_2O$ (50 mL) was added and the reaction mixture was extracted with EtOAc (3 x 100 mL), washed with $H_2O$ (4 x 100 mL), dried over $Na_2SO_4$, and filtered. The solvent was removed under reduced pressure affording the pure title compound **11** (436 mg, 1.702 mmol, 81%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.60 (dt, $^4J$ = 0.8 Hz, $^3J$ = 7.8 Hz, 1H, indole 4-H), 7.23-7.17 (m, 2H, indole 6-H, indole 7-H), 7.09 (dd, $^4J$ = 1.6 Hz, $^3J$ = 6.4 Hz, 1H, indole 5-H), 6.17 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.07 (dd, $^3J$ = 10.6 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 4.95 (dd, $^3J$ = 17.5 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 3.70 (s, 3H, CN(C$H_3$)C), 3.19 (t, $^3J$ = 7.7 Hz, 2H, $CH_3NHCH_2CH_2$C), 2.83 (t, $^3J$ = 7.7 Hz, 2H, $CH_3NHCH_2CH_2$C), 2.47 (s, 3H, $CH_2CH_2NHCH_3$), 1.70 (s, br, 1H, $CH_2CH_2NHCH_3$), 1.63 (s, 6H, C(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 147.9 ($C(CH_3)_2CH$=$CH_2$), 140.2 (indole C-2), 137.6 (indole C-7a), 128.8 (indole C-3a), 121.5 (indole C-6), 118.9 (indole C-5), 118.2 (indole C-4), 111.8 ($C(CH_3)_2CH$=$CH_2$), 109.8 (indole C-3), 108.5 (indole C-7), 54.3 ($CH_2CH_2NHCH_3$), 40.8 ($N(CH_3)CC(CH_3)_2CH$), 36.5 ($CH_2CH_2NHCH_3$), 33.2 ($CHCN(CH_3)CC$), 29.6 (2C, $C(CH_3)_2CH$=$CH_2$), 25.9 ($CCH_2CH_2NHCH_3$).

**IR** (ATR): $\tilde{\nu}$ = 3314 cm$^{-1}$ (w, br), 3050 (w), 2968 (w), 2933 (w), 2880 (w), 2791 (w), 1472 (s), 1355 (m), 1319 (m), 1233 (m), 1131 (w), 1109 (w), 1085 (w), 1015 (w), 995 (w), 912 (m), 739 (s), 707 (m), 686 (w), 562 (w).

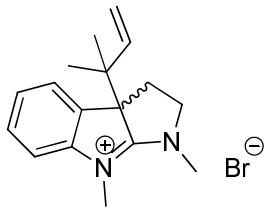
**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 290 nm (3.84), 240 (4.10), 232 (3.75).

**MS** (EI, 70 eV): *m/z* (%) = 256 $[M]^+$ (6), 213 $[M-(C_2H_5N)+H]^+$ (100), 212 $[M-C_2H_5N]^+$ (64), 199 (10), 198 $[M-C_3H_8N]^+$ (70), 182 (35).

**GC-HRMS** (EI): calcd. for $C_{17}H_{24}N_2$ $[M]^+$ 256.1934,

found 256.1961.

**1,8-Dimethyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*] indolium bromide (13)**



**13**

To a solution of $N_a$-methyldebromodeformylflustrabromine (**11**, 233 mg, 0.91 mmol, 1.0 eq.) in THF (16 mL) at 0 °C was added NBS (165 mg, 0.91 mmol, 1.0 eq.). After 20 min, the precipitate was washed with EtOAc (20 mL) and dried in vacuum to afford compound **13** (192 mg, 0.57 mmol, 63%) as a colourless amorphous solid.

**Mp**: 166 °C.

**$^1$H NMR** (400 MHz, $D_2O$): $\delta$ = 7.58 (dt, $^4J$ = 1.3 Hz, $^3J$ = 7.9 Hz, 1H, 6-H), 7.42 (dd, $^4J$ = 1.2 Hz, $^3J$ = 7.6 Hz, 1H, 4-H), 7.32-7.27 (m, 2H, 5-H, 7-H), 6.03 (dd, $^3J$ = 17.4, 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.26 (dd, $^3J$ = 10.8 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.21 (dd, $^3J$ = 17.4 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.56 (ddd, $^3J$ = 9.5, 6.3 Hz, $^2J$ = 11.7 Hz, 1H, =$CN(CH_3)NCH_2CH_2C$), 4.16 (ddd, $^3J$ = 11.5, 10.1 Hz, 1H, =$CN(CH_3)CH_2CH_2C$), 3.83 (s, 3H, $CN^+(CH_3)$=$CN(CH_3)$), 3.72 (s, 3H, $CN^+(CH_3)$=$CN(CH_3)$), 2.79 (dd, $^3J$ = 6.0 Hz, $^2J$ = 13.4, 1H, $N(CH_3)CH_2CH_2C$), 2.49 (dt, $^3J$ = 9.7, 3.6 Hz, $^2J$ = 13.3 Hz, 1H, $N(CH_3)CH_2CH_2C$), 1.14 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.96 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $D_2O$): $\delta$ = 180.9 (C-8a), 152.0 (C-7a), 144.6 ($C(CH_3)_2CH$=$CH_2$), 134.4 (C-3b), 132.5 (C-6), 127.9 (C-4), 126.8 (C-7), 118.7 ($C(CH_3)_2CH$=$CH_2$), 113.3 (C-5), 71.8 (C-3a), 68.0 (C-2), 48.8 ($N^+(CH_3)$=$CCC(CH_3)_2CH$=$CH_2$), 38.0 ($N^+(CH_3)$=$CN(CH_3)CH_2$), 34.0 ($N^+(CH_3)$=$CN(CH_3)CH_2$), 30.0 ($CCH_2CH_2N(CH_3)C$), 25.8 ($C(CH_3)_2CH$=$CH_2$), 24.7 ($C(CH_3)_2CH$=$CH_2$).

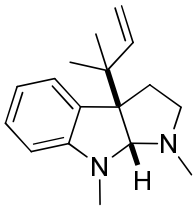
**IR** (ATR): $\tilde{\nu}$ = 3403 cm$^{-1}$ (w, br), 3328 (w), 3157 (w), 3080 (w), 3030 (w), 3006 (w), 2960 (w), 2895 (w), 2797 (w), 1772 (w), 1691 (s), 1608 (m), 1456 (m), 1433 (m), 1402 (m), 1373 (m), 1348 (w), 1329 (m), 1294 (m), 1178 (m), 1151 (m), 1105 (m), 1005 (w), 933 (m), 811 (m), 775 (s), 709 (w), 639 (m).

**UV** (DMSO): $\lambda_{max}$ (log ε) = 296 nm (3.39), 275 (3.55), 253 (3.51).

**MS** (ESI): *m/z* (%) = 255 $[M]^+$ (100), 186 $[M\text{-}C_5H_9]^+$ (16), 185 (5).

| | | |
|---|---|---|
| **HRMS** (ESI): | calcd. for $C_{17}H_{23}N_2^+$ $[M]^+$ | 255.1856, |
| | found | 255.1855. |
| EA: | calcd. for $C_{17}H_{23}BrN_2$ | C = 60.90, H = 6.91, N = 8.36 |
| | found | C = 60.59, H = 6.87, N = 8.34 |

**1,8-Dimethyl-3*a*-(2-methylbut-3-en-2-yl)-1,2,3,3*a*,8,8*a*-hexahydropyrrolo[2,3-*b*]indole (14)**



**14**

To the indole derivative **13** (40 mg, 0.12 mmol, 1.0 eq.) in MeOH (4 mL) was added $NaBH_4$ (3.2 mg, 0.08 mmol, 0.7 eq.) at rt. The reaction mixture was stirred under Ar for 7 h at rt and diluted cautiously with $H_2O$ (4 mL), followed by 2 N NaOH (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with $H_2O$ (3 x 50 mL), brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The resulting crude was purified by HPLC (RP-silica gel, MeOH/$H_2O$ (5:1)) to obtain the title compound **14** (11.3 mg, 0.04 mmol, 40%) as an oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.10-7.06 (m, 2H, 4-H, 6-H), 6.61 (dt, $^4J$ = 1.0 Hz, $^3J$ = 7.3 Hz, 1H, 5-H), 6.37 (d, $^3J$ = 7.5 Hz, 1H, 7-H), 5.96 (dd, $^3J$ = 17.6, 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.06 (dd, $^3J$ = 10.8 Hz, $^2J$ = 1.4 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 5.00 (dd, $^3J$ = 17.4 Hz, $^2J$ = 1.4 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 4.18 (s, 1H, 8a-H), 2.94 (s, 3H, $CN(CH_3)CHN(CH_3)CH_2$), 2.66 (ddd, $^3J$ = 4.7, 2.5 Hz, $^2J$ = 9.3, 1H, $CHN(CH_3)CH_2CH_2C$), 2.47-2.40 (m, 1H, $CHN(CH_3)CH_2CH_2C$), 2.44 (s, 3H, $CN(CH_3)CHN(CH_3)CH_2$), 2.26 (ddd, $^3J$ = 9.5, 6.6 Hz, $^2J$ = 11.9, 1H, $CHN(CH_3)CH_2CH_2C$), 1.81 (ddd, $^3J$ = 5.5, 2.9 Hz, $^2J$ = 11.9 Hz, 1H, $CHN(CH_3)CH_2CH_2C$), 1.02 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.91 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 153.2 (C-7a), 145.3 ($C(CH_3)_2CH$=$CH_2$), 133.2 (C-3b), 127.9 (C-6), 124.7 (C-4), 116.7 (C-5), 112.7 ($C(CH_3)_2CH$=$CH_2$), 106.1 (C-7), 91.2 (C-8a), 63.9 (C-3a), 53.4 (C-2), 41.1 ($NCHCC(CH_3)_2CH$=$CH_2$), 37.5 ($CN(CH_3)CHN(CH_3)CH_2$), 35.7 ($CN(CH_3)CHN(CH_3)CH_2$), 34.5 (C-3), 23.6 ($C(CH_3)_2CH$=$CH_2$), 22.6 ($C(CH_3)_2CH$=$CH_2$).

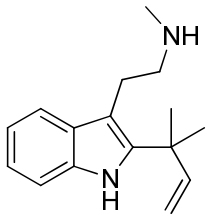
**IR** (ATR): $\tilde{\nu}$ = 3299 $cm^{-1}$ (w, br), 3131 (w), 2967 (m), 2724 (w), 1771 (w), 1697 (s), 1608 (m), 1456 (m), 1407 (m), 1370 (w), 1350 (m), 1331 (w), 1293 (w), 1240 (w), 1180 (m), 1150 (m), 1106 (m), 1010 (w), 936 (m), 914 (m), 851 (w), 815 (m), 762 (s), 710 (w), 691 (w), 635 (m), 605 (w), 540 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 296 nm (3.47), 276 (3.56), 239 (3.72), 233 (3.43).

**MS** (ESI): *m/z* (%) = 257 $[M+H]^+$ (2), 256 $[M]^+$ (19), 255 $[M-H]^+$ (100), 200 (5), 187 (7), 186 (52), 185 (25), 144 (4).

**HRMS** (ESI): calcd. for $C_{17}H_{24}N_2^+$ $[M-H]^+$ 255.1856,
found 255.1857.

### *N*-Methyl-2-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine (4)




**4**

To a solution of debromoflustrabromine (**2**, 1 g, 3.70 mmol, 1.0 eq.) in EtOH (150 mL) was added aqueous NaOH (32%, 11 mL). The reaction mixture was refluxed for 48 h and cooled to rt. $H_2O$ (100 mL) was added and the reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with $H_2O$ (4x 100 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure affording **4** (870 mg, 3.59 mmol, 97%) as an orange oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.89 (s, br, 1H, indole N*H*), 7.56 (dd, $^4J$ = 2.0 Hz, $^3J$ = 6.4 Hz, 1H, indole 4-H), 7.30 (dd, $^4J$ = 2.2 Hz, $^3J$ = 6.6 Hz, 1H, indole 7-H), 7.16-7.02 (m, 2H, indole 5-H, 6-H), 6.13 (dd, $^3J$ = 17.4, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.20-5.11 (m, 2H, $C(CH_3)_2CH$=$CH_2$), 3.09-2.98 (m, 2H, $CH_3NHCH_2CH_2C$), 2.89-2.81 (m, 2H, $CH_3NHCH_2CH_2C$), 2.48 (s, 3H, $CH_2CH_2NHCH_3$), 1.54 (s, 6H, $C(CH_3)_2CH$=$CH_2$), 1.50 (s, br, 1H, $CCH_2CH_2NH$ $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 146.0 ($C(CH_3)_2CH$=$CH_2$), 139.5 (indole C-2), 134.1 (indole C-7a), 129.8 (indole C-3a), 121.3 (indole C-6), 119.1 (indole C-5), 118.3 (indole C-4), 111.9 ($C(CH_3)_2CH$=$CH_2$), 110.3 (indole C-7), 109.0 (indole C-3), 53.1 ($CH_2CH_2NHCH_3$), 39.0 ($NHCC(CH_3)_2CH$), 36.5 ($CH_2CH_2NHCH_3$), 27.7 (2C, $C(CH_3)_2CH$=$CH_2$), 25.6 ($CCH_2CH_2NHCH_3$).

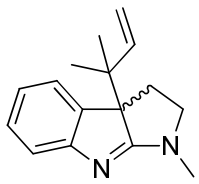
**IR** (ATR): $\tilde{\nu}$ = 3434 $cm^{-1}$ (w), 3298 (w, br), 3185 (w, br), 3080 (w), 3056 (w), 2967 (m), 2932 (w), 2870 (w), 2798 (w), 1632 (w), 1460 (m), 1360 (w), 1339 (w), 1303 (w), 1232 (w), 1129 (w), 1103 (w), 1008 (m), 914 (m), 738 (s), 597 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 283 nm (3.86), 239 (3.98), 233 (3.79).

**MS** (EI, 70 eV): *m/z* (%) = 242 $[M]^+$ (5), 199 (100), 184 $[M-C_3H_8N]^+$ (83), 172 $[M-C_5H_9]^+$ (7), 168 (44.

**GC-HRMS** (EI): calcd. for $C_{16}H_{22}N_2$ $[M]^+$ 242.1778,,
found 242.1758.

**1-Methyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (*rac*-Debromoflustramine C, 6)**



**6**

To a solution of debromodeformylflustrabromine (**4**, 200 mg, 0.83 mmol, 1.0 eq.) in THF (20 mL) was added NBS (147 mg, 0.83 mmol, 1.0 eq.). The reaction mixture was stirred at 0 °C for 1 h and diluted with $Et_2O$ (50 mL). The organic layer was washed with 2 N NaOH (3x 50 mL) and with $H_2O$ (3x 50 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, EtOAc) affording *rac*-debromoflustramine C (**6**, 156 mg, 0.61 mmol, 71%) as a colourless oil.

**TLC** [silica gel, EtOAc]: $R_f$ = 0.23.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.17 (dt, $^4J$ = 1.3 Hz, $^3J$ = 7.6 Hz, 1H, 6-H), 7.11 (dd, $^4J$ = 0.8 Hz, $^3J$ = 7.8 Hz, 1H, 5-H), 7.09-7.07 (m, 1H, 4-H), 6.80 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.4 Hz, 1H, 7-H), 6.08-6.01 (m, 1H, $C(CH_3)_2CH$=$CH_2$), 5.07 (s, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.04 (dd, $^3J$ = 7.0 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 3.95 (ddd, $^3J$ = 6.3, 3.9 Hz, $^2J$ = 12.7 Hz, 1H, $(CH_3)NCH_2CH_2C$), 3.40 (dt, $^3J$ = 10.1, 1.0 Hz, 1H, $(CH_3)NCH_2CH_2C$), 3.05 (s, 3H, $NCH_3$), 2.39 (ddd, $^3J$ = 6.1, 0.7 Hz, $^2J$ = 13.1 Hz, 1H, $(CH_3)NCH_2CH_2C$), 2.11 (ddd, $^3J$ = 7.7, 5.8 Hz, $^2J$ = 16.0 Hz, 1H, $(CH_3)NCH_2CH_2C$), 1.01 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.87 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 187.0 (C-8a), 160.8 (C-7a), 143.7 ($C(CH_3)_2CH=CH_2$), 138.2 (C-3b), 128.5 (C-6), 123.5 (C-4), 119.6 (C-7), 115.7 (C-5), 113.3 ($C(CH_3)_2CH=CH_2$), 66.1 (C-3a), 59.9 (C-2), 43.1 ($N=CCC(CH_3)_2CH=CH_2$), 33.4 ($NCH_3$), 27.9 (C-3), 22.8 ($C(CH_3)_2CH=CH_2$), 21.6 ($C(CH_3)_2CH=CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3059 cm$^{-1}$ (w), 2969 (w), 2930 (w), 2877 (w), 2796 (w), 1633 (s), 1576 (s), 1446 (m), 1412 (m), 1380 (w), 1364 (w), 1307 (w), 1278 (m), 1216 (m), 1181 (m), 1154 (w), 1103 (w), 1007 (w), 987 (w), 915 (m), 848 (w), 818 (w), 765 (s), 747 (s), 685 (w), 656 (w).

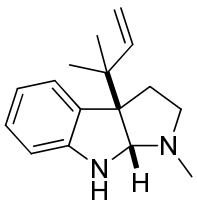
**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 283 nm (3.83), 239 (3.62), 231 (3.55).

**MS** (EI, 70 eV): *m/z* (%) = 240 $[M]^+$ (15), 172 $[M-(C_5H_9)+H]^+$ (30), 171 $[M-C_5H_9]^+$ (100), 130 (30).

**GC-HRMS** (EI): calcd. for $C_{16}H_{20}N_2$ $[M]^+$ 240.1621,

found 240.1638.

**1-Methyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b] indole (*rac*-Debromodihydroflustramine C, 8)**



**8**

At rt, DIBAL-H (1.0 M in toluene, 0.61 mL, 0.61 mmol, 1.85 eq.) was added drop wise to a solution of *rac*-debromoflustramine C (**6**, 80 mg, 0.33 mmol, 1.0 eq.) in THF (5 mL) under Ar. The reaction mixture was stirred at rt for 24 h and added drop wise to ice water (60 mL). $Et_2O$ (30 mL) was added, followed by aqueous NaOH (12 M, 20 mL). After extraction with $Et_2O$ (3 x 20 mL), the combined ethereal layers were washed with $H_2O$ (3 x 30 mL) and brine (20 mL), and dried over $Na_2SO_4$. Concentration in vacuum and column chromatography (silica gel, $CHCl_3$/MeOH (5:1)) afforded *rac*-debromodihydroflustramine C (**8**, 58 mg, 0.24 mmol, 73%) as a yellow oil.

**TLC** [silica gel, $CHCl_3$/MeOH (5:1)]: $R_f$ = 0.2.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.13 (ddd, $^4J$ = 0.4, 1.2 Hz, $^3J$ = 7.5 Hz, 1H, 4-H), 7.08 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.6 Hz, 1H, 6-H), 6.74 (dt, $^4J$ = 1.0 Hz, $^3J$ = 7.5 Hz, 1H, 5-

H), 6.65 (d, $^3J$ = 7.8 Hz, 1H, 7-H), 5.99 (dd, $^3J$ = 17.4, 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.10 (dd, $^3J$ = 1.3 Hz, $^2J$ = 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.03 (dd, $^3J$ = 1.3 Hz, $^2J$ = 17.3 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.82 (s, br, 1H, 8a-H), 2.993-2.92 (m, 1H, $(CH_3)NCH_2CH_2C$), 2.59-2.51 (m, 1H, $(CH_3)NCH_2CH_2C$), 2.54 (s, 3H, $NCH_3$), 2.45 (ddd, $^3J$ = 9.5, 6.5 Hz, $^2J$ = 12.2, 1H, $(CH_3)NCH_2CH_2C$), 1.98 (ddd, $^3J$ = 5.7, 3.2 Hz, $^2J$ = 12.4 Hz, 1H, $(CH_3)NCH_2CH_2C$), 1.08 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 1.03 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 150.0 (C-7a), 144.3 ($C(CH_3)_2CH$=$CH_2$), 132.2 (C-3b), 128.3 (C-6), 125.0 (C-4), 118.9 (C-5), 113.7 ($C(CH_3)_2CH$=$CH_2$), 109.4 (C-7), 88.4 (C-8a), 64.5 (C-3a), 53.2 (C-2), 41.3 ($NHCHC(CH_3)_2CH$=$CH_2$), 36.3 ($NCH_3$), 33.9 (C-3), 23.2 ($C(CH_3)_2CH$=$CH_2$), 22.5 ($C(CH_3)_2CH$=$CH_2$).

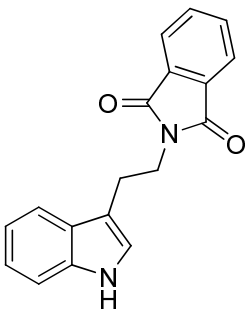
**IR** (ATR): $\tilde{\nu}$ = 3259 cm$^{-1}$ (w, br), 3082 (w), 2964 (m), 2932 (m), 2872 (w), 2790 (w), 2659 (w), 2469 (w), 1669 (w), 1604 (m), 1483 (m), 1467 (s), 1414 (w), 1381 (w), 1365 (w), 1350 (w), 1316 (w), 1257 (w), 1153 (m), 1077 (w), 1004 (m), 913 (m), 740 (s), 689 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 294 nm (3.37), 243 (3.75).

**MS** (EI, 70 eV): *m/z* (%) = 242 $[M]^+$ (22), 174 $[M-(C_5H_9)+H]^+$ (24), 173 $[M-C_5H_9]^+$ (100), 130 (42).

**GC-HRMS** (EI): calcd. for $C_{16}H_{22}N_2$ $[M]^+$ 242.1778,
found 242.1762.

**2-(2-(1*H*-Indol-3-yl)ethyl)isoindoline-1,3-dione (165)**



**165**

Phthalic anhydride (4.03 g, 27.0 mmol, 1.1 eq.) was added to a solution of tryptamine (**124**, 3.9 g, 24.33 mmol, 1.0 eq.) in toluene (50 mL), followed by addition of $Et_3N$ (3.75 mL, 27.0 mmol, 1.1 eq.). The reaction mixture was refluxed at 125 °C for 8 h, cooled to rt and added to ice water (100 mL). The yellow precipitate was recrystallized from MeOH (5 mL of MeOH/g) to obtain compound **165** (5.52 g, 19.01 mmol, 77%) as a brown solid.

**Mp**: 164-166 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.01 (s, br, 1H, indole N*H*), 7.82 (dd, $^3J$ = 5.8, 3.2 Hz, 2H, N(C(=O)CC*H*CH)$_2$), 7.73 (d, $^3J$ = 8.32 Hz, 1H, indole 4-H), 7.69 (dd, $^3J$ = 5.8, 3.1 Hz, 2H, N(C(=O)CCHC*H*)$_2$), 7.34 (d, $^3J$ = 7.8 Hz, 1H, indole 7-H), 7.17 (ddd, $^3J$ = 13.7, 6.1 Hz, $^2J$ = 1.3 Hz, 1H, indole 6-H), 7.10 (dd, $^3J$ = 7.0 Hz, $^4J$ = 1.2 Hz, 1H, indole 5-H), 7.08 (s, 1H, indole 2-H), 4.00 (t, $^3J$ = 7.8 Hz, 2H, $CCH_2CH_2$N), 3.15 (t, $^3J$ = 7.8 Hz, 2H, $CCH_2CH_2$N).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.4 (2C, N(*C*(=O)CCHCH)$_2$), 136.2 (indole C-7a), 133.8 (2C, N(C(=O)CCH*C*H)$_2$), 132.2 (2C, N(C(=O)*C*CHCH)$_2$), 127.4 (indole C-3a), 123.2 (2C, N(C(=O)C*C*HCH)$_2$), 122.1 (indole C-6), 122.0 (indole C-2), 119.5 (indole C-5), 118.9 (indole C-4), 112.5 (indole C-3), 111.1 (indole C-7), 38.5 ($CNHCHCCH_2CH_2$N), 24.5 ($CNHCHCCH_2CH_2$N).

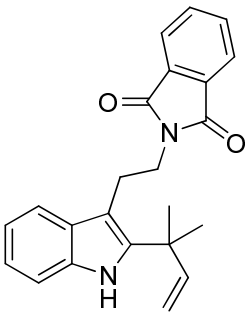
**IR** (ATR): $\tilde{\nu}$ = 3379 cm$^{-1}$ (m), 3352 (br, m), 3043 (w), 2979 (w), 2861 (w), 1767 (m), 1696 (s, br), 1617 (m), 1460 (m), 1430 (m), 1395 (s), 1355 (m), 1327 (m), 1230 (m), 1186 (w), 1169 (w), 1097 (m), 1058 (m), 1011 (w), 985 (m), 867 (m), 821 (w), 741 (s), 707 (s), 654 (m), 632 (m), 586 (m), 529 (s).

**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 354 nm (2.28), 289 (3.80), 281 (3.84), 240 (4.10), 220 (4.84), 194 (4.49).

**MS** (EI, 70 eV): *m/z* (%) = 290 $[M]^+$ (29), 143 (36), 130 $[M\text{-}C_9H_6NO_2]^+$ (100), 77 (11).

**GC-HRMS** (EI): calcd. for $C_{18}H_{14}N_2O_2$ $[M]^+$ 290.1050,
found 290.1071.

**2-(2-(2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (166)**



**166**

To a solution of **165** (2.2 g, 7.58 mmol, 1.0 eq.) in THF (45 mL) and $Et_3N$ (1.4 mL, 10.34 mmol, 1.2 eq.) was added *tert*-BuOCl (1.17 mL, 10.34 mmol, 1.2 eq.) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C, before a freshly prepared solution of prenyl-9-BBN (**142**, 0.5 M, 34.5 mL, 17.24 mmol, 2.0 eq.) in THF was added drop wise. After 30 min the reaction mixture was allowed to warm to rt and was stirred for 1 h. Aqueous NaOH (3 M, 18 mL) and $H_2O_2$ (30%, 18 mL) were added drop wise. The

reaction mixture was stirred at rt for 1 h and diluted in $Et_2O$ (200 mL). The organic layer was washed three times with brine-water (1:1, 150 mL) , dried over $MgSO_4$, filtered, and concentrated in vacuum. The residual yellow oil was recrystallized from $CHCl_3$/hexane (1:5, 30 mL) to afford compound **166** (1.37 g, 3.83 mmol, 50%) as a yellow amorphous solid.

**Mp**: 143-146 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.91 (s, br, 1H, indole N*H*), 7.88-7.83 (m, 2H, N(C(=O)CC*H*CH)$_2$), 7.79-7.77 (m, 1H, indole 4-H), 7.73-7.68 (m, 2H, N(C(=O)CCHC*H*)$_2$), 7.32-7.27 (m, 1H, indole 7-H), 7.16-7.10 (m, 2H, indole 5-H, indole 6-H), 6.17 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, C(CH$_3$)$_2$C*H*=CH$_2$), 5.22 (dd, $^3J$ = 10.4 Hz, $^2J$ = 1.0 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_Z$), 5.19 (dd, $^3J$ = 3.5 Hz, $^2J$ = 1.0 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_E$), 3.93-3.89 (m, 2H, CCH$_2$C*H*$_2$N), 3.20-3.15 (m, 2H, CC*H*$_2$CH$_2$N), 1.62 (s, 6H, C(C*H*$_3$)$_2$CH=CH$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.3 (2C, N(*C*(=O)CCHCH)$_2$), 145.6 (C(CH$_3$)$_2$*C*H=CH$_2$), 140.1 (indole C-2), 134.1 (indole C-7a), 133.8 (2C, N(C(=O)CCH*C*H)$_2$), 132.3 (2C, N(C(=O)*C*CHCH)$_2$), 129.6 (indole C-3a), 123.1 (2C, N(C(=O)C*C*HCH)$_2$), 121.5 (indole C-6), 119.6 (indole C-5), 118.3 (indole C-4), 112.3 (C(CH$_3$)$_2$CH=*C*H$_2$), 110.4 (indole C-7), 107.1 (indole C-3), 38.9 (CNHC*C*(CH$_3$)$_2$CH), 38.4 (CNHCCCH$_2$*C*H$_2$N), 27.7 (2C, C(*C*H$_3$)$_2$CH=CH$_2$), 24.6 (CNHCC*C*H$_2$CH$_2$N).

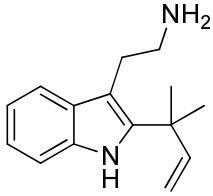
**IR** (ATR): $\tilde{\nu}$ = 3355 cm$^{-1}$ (m), 3084 (w), 3031 (w), 2970 (w), 2936 (w), 2867 (w), 1766 (w), 1696 (s), 1463 (m), 1430 (w), 1394 (s), 1354 (m), 1336 (m), 1245 (w), 1170 (w), 1103 (m), 1017 (m), 920 (m), 898 (w), 871 (m), 747 (s), 714 (s, br), 608 (m), 566 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (lg $\varepsilon$) = 283 nm (3.97), 242 (4.21).

**MS** (EI, 70 eV): *m/z* (%) = 358 [M]$^+$ (100), 290 [M-(C$_5$H$_9$)+H]$^+$ (12), 289 [M-C$_5$H$_9$]$^+$ (25), 210 (32).

**HRMS** (EI): calcd. for $C_{23}H_{22}N_2O_2$ [M]$^+$ 358.1676,
found 358.1676.

**2-(2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine (16)**



**16**

To a solution of $N_b$-phthaloyl-2-*tert.*-prenyl-tryptamine (**166**, 1.0 g, 2.79 mmol, 1.0 eq.) in DCM/MeOH (1:1, 30 mL) was added $NH_2NH_2$-$H_2O$ (0.38 mL, 7.82 mmol, 2.8 eq.) at rt. The reaction mixture was stirred for 48 h and poured into $H_2O$ (60 mL). After extraction with $Et_2O$ (4 x 100 mL), the organic extract was washed with HCl (1 N, 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. Chromatography of the residual oil (silica gel, $CHCl_3$/MeOH (6:1)) afforded compound **166** (0.43 g, 1.61 mmol, 58%) as a colourless oil.

**TLC** [silica gel, $CHCl_3$/MeOH (6:1)]: $R_f$ = 0.23.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.90 (s, br, 1H, indole N*H*), 7.55 (d, $^3J$ = 7.8 Hz, 1H, indole 4-H), 7.28 (dt, $^4J$ = 0.9 Hz, $^3J$ = 7.8 Hz, 1H, indole 7-H), 7.12 (dt, $^4J$ = 1.3 Hz, $^3J$ = 7.5 Hz, 1H, indole 6-H), 7.07 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 6.13 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.17 (dd, $^3J$ = 9.4 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 5.14 (dd, $^3J$ = 2.5 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 3.02 (s, br, 4H, $CCH_2CH_2NH_3^+Cl$), 2.34 (s, br, 3H, $CCH_2CH_2NH_3^+Cl$), 1.54 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 146.0 ($C(CH_3)_2CH$=$CH_2$), 139.7 (indole C-2), 134.1 (indole C-7a), 129.8 (indole C-3a), 121.4 (indole C-6), 119.2 (indole C-5), 118.3 (indole C-4), 112.0 ($C(CH_3)_2CH$=$CH_2$), 110.4 (indole C-7), 108.4 (indole C-3), 43.0 (2C, CNHCC$CH_2CH_2$N), 39.0 (CNHC$C(CH_3)_2CH$), 27.8 (2C, $C(CH_3)_2CH$=$CH_2$).

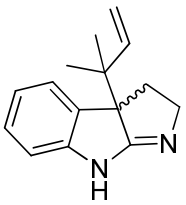
**IR** (ATR): $\tilde{\nu}$ = 3432 cm$^{-1}$ (w), 3140 (w), 3057 (w), 2965 (m), 2928 (m), 2871 (m), 1585 (m), 1460 (m), 1360 (w), 1340 (w), 1306 (m), 1228 (w), 1031 (w), 1009 (m), 905 (s, br), 734 (s, br).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 283 nm (3.83), 240 (3.92).

**MS** (EI, 70 eV): *m/z* (%) = 229 $[M+H]^+$ (4), 228 $[M]^+$ (23), 198 (100), 183 (56), 168 (41).

**GC-HRMS** (EI): calcd. for $C_{15}H_{20}N_2$ $[M]^+$ 228.1621,
found 228.1630.

**3*a*-(2-Methylbut-3-en-2-yl)-2,3,3*a*,8-tetrahydropyrrolo[2,3-*b*]indole (17)**



**17**

To a solution of 2-*tert*-prenyl-tryptamine (**16**, 100 mg, 0.38 mmol, 1.0 eq.) in THF (15 mL) was added NBS (79 mg, 0.44 mmol, 1.16 eq.) at rt. The reaction mixture was stirred at 0 °C for 35 min, before $CHCl_3$ (50 mL) was added. The organic layer was washed with 2 N NaOH (3 x 40 mL) and $H_2O$ (3 x 40 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residual green solid was purified by column chromatography (silica gel, $CHCl_3$/MeOH (7:1 to 5:1)) to afford compound **17** (47 mg, 0.21 mmol, 55%) as a green amorphous solid.

**TLC** [silica gel, $CHCl_3$/MeOH (5:1)]: $R_f$ = 0.45.

**Mp**: 160 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.28 (s, br, 8-H), 7.17 (dt, $^4J$ = 1.3 Hz, $^3J$ = 7.7 Hz, 1H, 6-H), 7.11 (dd, $^4J$ = 0.8 Hz, $^3J$ = 7.4 Hz, 1H, 4-H), 6.89 (dd, $^4J$ = 1.1 Hz, $^3J$ = 8.3 Hz, 1H, 5-H), 6.86 (dd, $^4J$ = 1.0 Hz, $^3J$ = 7.5 Hz, 1H, 7-H), 6.03 (dd, $^3J$ = 17.1, 11.0 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.05 (s, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.01 (dd, $^3J$ = 8.0 Hz, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 3.93 (ddd, $^3J$ = 9.3, 5.8 Hz, $^2J$ = 12.4 Hz, 1H, CNHC=NC$H_2CH_2$C), 3.82 (dd, $^3J$ = 9.0 Hz, $^2J$ = 12.4 Hz, 1H, CNHC=NC$H_2CH_2$C), 2.43 (dd, $^3J$ = 5.2 Hz, $^2J$ = 13.0 Hz, 1H, CNHC=N$CH_2CH_2$C), 2.13 (dt, $^3J$ = 6.4 Hz, $^2J$ = 16.7 Hz, 1H, CNHC=N$CH_2CH_2$C), 1.03 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 0.95 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 183.1 (C-8a), 152.5 (C-7a), 143.6 ($C(CH_3)_2CH$=$CH_2$), 134.4 (C-3b), 128.3 (C-6), 124.7 (C-4), 120.4 (C-7), 113.2 ($C(CH_3)_2CH$=$CH_2$), 112.0 (C-5), 65.5 (C-3a), 57.5 (C-2), 43.4 (CNHC(=N)C$C(CH_3)_2CH$), 32.1 (C-3), 22.9 ($C(CH_3)_2CH$=$CH_2$), 21.9 ($C(CH_3)_2CH$=$CH_2$).

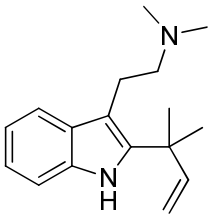
**IR** (ATR): $\tilde{\nu}$ = 3053 cm$^{-1}$ (w), 2968 (m), 2929 (m), 2874 (m), 2819 (m), 2738 (w), 1672 (s), 1638 (w), 1608 (m), 1455 (s), 1419 (m), 1380 (w), 1331 (m), 1233 (m), 1196 (m), 1153 (m), 1106 (m), 999 (m), 921 (s), 816 (m), 798 (w), 741 (s), 708 (s), 654 (m), 610 (m), 539 (m).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 258 nm (3.73).

**MS** (EI, 70 eV): *m/z* (%) = 226 $[M]^+$ (20), 157 $[M\text{-}C_5H_9]^+$ (100), 156 (30), 130 (32).

**HRMS** (EI): calcd. for $C_{15}H_{18}N_2$ $[M]^+$ 226.1465,
found 226.1464.

### *N*,*N*-Dimethyl-2-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine (20)



**20**

At rt, DIBAL-H (17% in toluene, 6.22 mL, 6.218 mmol, 4.2 eq.) was added drop wise to a solution of debromoflustrabromine (**2**, 400 mg, 1.48 mmol, 1.0 eq.) in THF (10 mL) under Ar. After 24 h, the reaction mixture was added in portions to ice water (150 mL). Aqueous HCl (12 M, 10 mL) was added at 0 °C (pH 2) and the organic layer was extracted with $Et_2O$ (3x 30 mL). The aqueous layer was brought to pH 11 by addition of aqueous NaOH (12 M, 20 mL) and was extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL), dried over $Na_2SO_4$, and concentrated in vacuum to afford compound **20** (325 mg, 1.27 mmol, 86%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.83 (s, br, 1H, indole N*H*), 7.53 (d, $^3J$ = 7.5 Hz, 1H, indole 4-H), 7.27 (dd, $^4J$ = 1.2 Hz, $^3J$ = 7.6 Hz, 1H, indole 7-H), 7.12 (dt, $^4J$ = 1.4 Hz, $^3J$ = 7.5 Hz, 1H, indole 6-H), 7.07 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 6.13 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.17 (dd, $^3J$ = 17.4 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 5.15 (dd, $^3J$ = 10.5 Hz, $^2J$ = 1.1 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 3.04-3.00 (m, 2H, $CCH_2CH_2N(CH_3)_2$), 2.56-2.47 (m, 2H, $CCH_2CH_2N(CH_3)_2$), 2.35 (s, 6H, $CCH_2CH_2N(CH_3)_2$), 1.54 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 145.9 ($C(CH_3)_2CH$=$CH_2$), 139.3 (indole C-2), 134.2 (indole C-7a), 129.7 (indole C-3a), 121.3 (indole C-6), 119.2 (indole C-5), 118.1 (indole C-4), 112.0 ($C(CH_3)_2CH$=$CH_2$), 110.4 (indole C-7), 108.9 (indole C-3), 60.4 ($CCH_2CH_2N(CH_3)_2$), 45.5 (2C, $CCH_2CH_2N(CH_3)_2$), 38.9 ($NHCC(CH_3)_2CH$), 27.7 (2C, $C(CH_3)_2CH$=$CH_2$), 23.4 ($CCH_2CH_2N(CH_3)_2$).

**IR** (ATR): $\tilde{\nu}$ = 3434 $cm^{-1}$ (w), 3255 (w, br), 3055 (w), 2968 (m), 2936 (m), 2867 (w), 2828 (w), 2789 (w), 1638 (w), 1459 (s), 1360 (w), 1341 (w), 1302 (w), 1247 (w), 1229 (w), 1137 (w), 1098 (w), 1029 (m), 1008 (m), 736 (s), 597 (m).

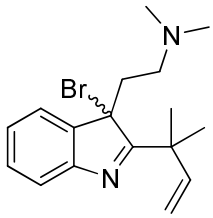
**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 284 nm (3.87), 240 (3.98).

**MS** (EI, 70 eV): *m/z* (%) = 256 $[M]^+$ (7), 198 $[M-C_3H_8N]^+$ (10), 183 $[M-(C_4H_{10}N)+H]^+$ (10), 58 (100).

**GC-HRMS** (EI): calcd. for $C_{17}H_{24}N_2$ $[M]^+$ 256.1934,

found 256.1944.

**2-(3-Bromo-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)-*N*,*N*-dimethylethanamine (21, NMR experiment)**



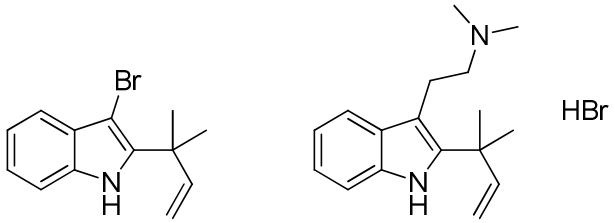

**21**

To a solution of $N_b$,$N_b$-dimethyl-2-*tert.*-prenyl-tryptamine (**20**, 60 mg, 0.23 mmol, 1.0 eq.) in acetone-$d_6$ (0.6 mL, NMR tube) was added NBS (42 mg, 0.23 mmol, 1.0 eq.) at rt. The NMR tube was shaken for 5 min and after 25 min the NMR spectrum was recorded.

**$^1$H NMR** (400 MHz, acetone-$d_6$): $\delta$ = 7.53 (d, $^3J$ = 7.4 Hz, 1H, indole 4-H), 7.47 (d, $^3J$ = 6.7 Hz, 1H, indole 7-H), 7.38 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.6 Hz, 1H, indole 6-H), 7.30 (dt, $^4J$ = 1.1 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 6.55 (dd, $^3J$ = 17.5, 10.7 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.30 (d, $^3J$ = 17.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 5.19 (d, $^3J$ = 10.6 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 2.88-2.75 (m, 2H, $CCH_2CH_2N(CH_3)_2$), 2.68 (s, 4H, $(CH_2CO)_2NH$), 2.01 (s, 6H, $CCH_2CH_2N(CH_3)_2$), 1.97-1.88 (m, 1H, $CCH_2CH_2N(CH_3)_2$), 1.71-1.65 (m, 1H, $CCH_2CH_2N(CH_3)_2$), 1.67 (s, 3H, $C(CH_3)_2CH$=$CH_2$), 1.62 (s, 3H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, acetone-$d_6$): $\delta$ = 186.6 (indole C-2), 179.0 (2C, $(CH_2CO)_2NH$), 151.9 (indole C-7a), 145.0 ($C(CH_3)_2CH$=$CH_2$), 141.2 (indole C-3a), 130.5 (indole C-6), 127.6 (indole C-5), 123.3 (indole C-4), 121.3 (indole C-7), 113.5 ($C(CH_3)_2CH$=$CH_2$), 63.9 (indole C-3), 54.9 ($CCH_2CH_2N(CH_3)_2$), 45.1 (2C, $CCH_2CH_2N(CH_3)_2$), 44.3 (N=$CC(CH_3)_2CH$=$CH_2$), 37.8 ($CCH_2CH_2N(CH_3)_2$), 30.2 (2C, $CH_2CO)_2NH$), 29.6 ($C(CH_3)_2CH$=$CH_2$), 27.7 ($C(CH_3)_2CH$=$CH_2$).

**3-Bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indole (22) and *N*,*N*-dimethyl-2-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine hydrobromide (23)**




**22** **23**

To a solution of $N_b$,$N_b$-dimethyl-2-*tert.*-prenyl-tryptamine (**20**, 400 mg, 1.56 mmol, 1.0 eq.) in acetone (20 mL) was added NBS (308 mg, 1.72 mmol, 1.1 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 50 min and diluted with $Et_2O$ (100 mL). The reaction mixture was washed twice with 2N NaOH (2 x 50 mL), followed by extraction with $H_2O$ (3 x 50 mL). The organic layer was dried over $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH (9:1)) to afford compound **22** (88 mg, 0.33 mmol, 21%) as a dark green oil and compound **23** (305 mg, 0.91 mmol, 58%) as a yellow oil.

3-Bromoindole **22**

**TLC** [silica gel, acetone/petrolether (1:2)]: $R_f$ = 0.73.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.07 (s, br, 1H, indole N*H*), 7.55-7.50 (m, 1H, indole 4-H), 7.30-7.26 (m, 1H, indole 7-H), 7.20-7.13 (m, 2H, indole 5-H, indole 6-H), 6.17 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.24 (dd, $^3J$ = 7.0 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_Z$), 5.21 (dd, $^3J$ = 13.4 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH$=C$H_2$-$H_E$), 1.63 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 144.3 ($C(CH_3)_2$*C*H=$CH_2$), 139.5 (indole C-2), 133.3 (indole C-7a), 129.0 (indole C-3a), 122.5 (indole C-6), 120.4 (indole C-5), 118.6 (indole C-4), 113.5 ($C(CH_3)_2CH$=*C*$H_2$), 110.7 (indole C-7), 87.9 (indole C-3), 39.0 (NHC*C*$(CH_3)_2CH$), 26.4 (2C, C(*C*$H_3)_2CH$=$CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3151 $cm^{-1}$ (w, br), 3059 (w, br), 2964 (m), 2925 (m), 1704 (w), 1641 (w), 1617 (m), 1455 (m), 1385 (w), 1363 (w), 1259 (w), 1211 (w), 1101 (m), 1011 (m), 913 (w), 802 (m), 746 (s).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 557 nm (3.02), 428 (3.16), 354 (3.25), 279 (3.86), 272 (3.87), 240 (3.99).

**MS** (EI, 70 eV): *m/z* (%) = 263 $[M]^+$ (24), 169 (100), 167 (18), 127 (31).

**GC-HRMS** (EI): calcd. for $C_{13}H_{14}N_2Br^{79}$ $[M]^+$ 263.0304,
found 263.0295.

Hydrobromide **23**

**TLC** [silica gel, acetone/petrolether (1:2)]: $R_f$ = 0.49.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.15 (s, br, 1H, indole N*H*), 7.57 (d, $^3J$ = 7.6 Hz, 1H, indole 4-H), 7.35 (dd, $^4J$ = 1.3 Hz, $^3J$ = 7.5 Hz, 1H, indole 7-H), 7.14 (dt, $^4J$ = 1.4 Hz, $^3J$ = 7.5 Hz, 1H, indole 6-H), 7.09 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 6.10 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.17 (dd, $^3J$ = 14.4 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 5.15 (dd, $^3J$ = 7.4 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 3.32-3.28 (m, 2H, $CCH_2CH_2N(CH_3)_2$), 3.00-2.96 (m, 2H, $CCH_2CH_2N(CH_3)_2$), 2.72 (s, 6H, $CCH_2CH_2N(CH_3)_2$), 1.54 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 145.6 ($C(CH_3)_2CH$=$CH_2$), 140.3 (indole C-2), 134.2 (indole C-7a), 128.8 (indole C-3a), 121.7 (indole C-6), 119.7 (indole C-5), 117.7 (indole C-4), 112.2 ($C(CH_3)_2CH$=$CH_2$), 110.8 (indole C-7), 105.2 (indole C-3), 58.2 ($CCH_2CH_2N(CH_3)_2$), 43.3 (2C, $CCH_2CH_2N(CH_3)_2$), 38.8 ($NHCC(CH_3)_2CH$), 27.7 (2C, $C(CH_3)_2CH$=$CH_2$), 20.9 ($CCH_2CH_2N(CH_3)_2$).

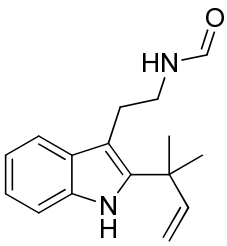
**IR** (ATR): $\tilde{\nu}$ = IR (ATR): $\tilde{\nu}$ = 3270 $cm^{-1}$ (w, br), 2966 (w, br), 2666 (w, br), 2462 (w), 1469 (s), 1342 (w), 1307 (w), 1236 (w), 1008 (m), 956 (m), 918 (m), 744 (s), 716 (m).

**UV** ($CH_2Cl_2$): $\lambda_{max}$ (log ε) = 282 nm (3.86), 239 (3.91), 233 (3.68).

**MS** (ESI): *m/z* (%) = 257 $[M]^+$ (67), 212 $[M-C_2H_7N]^+$ (100).

**HRMS** (ESI): calcd. for $C_{17}H_{25}N_2$ $[M]^+$ 257.2012,
found 257.2011.

***N*-(2-(2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)formamide (18)**



**18**

A mixture of $Ac_2O$ (0.23 mL, 2.42 mmol, 2.5 eq.) and $HCO_2H$ (0.1 mL, 2.42 mmol, 2.5 eq.) was stirred at 60 °C for 1 h. After cooling to rt, a solution of 2-*tert*-prenyltryptamine (**16**, 221 mg, 0.97 mmol, 1.0 eq.) in DCM (10 mL) was added drop wise. The reaction mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was added to aqueous NaOH (12 M, 14 mL) and ice (15 g). The alkaline mixture was diluted with DCM (50 mL) and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were washed with HCl (2M, 2 x 30 mL), $H_2O$ (3 x 50 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum to afford compound **18** (240 mg, 0.94 mmol, 97%) as an oil.

Ratio of rotamers in $CDCl_3$: 1:0.2.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.12 (s, 1H, C*H*O), 8.02 (s, br, 1H, indole N*H*), 7.55 (dt, $^4J$ = 0.5 Hz, $^3J$ = 7.7 Hz, 1H, indole 4-H), 7.30 (dt, $^4J$ = 0.9 Hz, $^3J$ = 8.0 Hz, 1H, indole 7-H), 7.14 (td, $^4J$ = 1.3 Hz, $^3J$ = 7.4 Hz, 1H, indole 6-H), 7.09 (td, $^4J$ = 1.2 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 6.12 (dd, $^3J$ = 17.7, 10.3 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.67 (s, br, 1H, $CH_2NH$CHO), 5.17 (dd, $^3J$ = 6.2 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.14 (d, $^2J$ = 1.2 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 3.58 (q, $^3J$ = 13.8, 6.9 Hz, 2H, $CCH_2CH_2$NHCHO), 3.08 (t, $^3J$ = 7.3 Hz, 2H, $CCH_2CH_2$NHCHO), 1.54 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 161.2 (*C*HO), 145.8 ($C(CH_3)_2CH$=$CH_2$), 140.2 (indole C-2), 134.2 (indole C-7a), 129.6 (indole C-3a), 121.5 (indole C-6), 119.6 (indole C-5), 118.1 (indole C-4), 112.1 ($C(CH_3)_2CH$=$CH_2$), 110.5 (indole C-7), 107.4 (indole C-3), 39.0 (NHC*C*$(CH_3)_2CH$), 38.8 ($CCH_2CH_2$NHCHO), 27.8 (2C, $C(CH_3)_2CH$=$CH_2$), 24.9 ($CCH_2CH_2$NHCHO).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.97 (s, 1H, C*H*O), 7.94 (s, br, 1H, indole N*H*), 7.45 (dt, $^4J$ = 0.6 Hz, $^3J$ = 7.8 Hz, 1H, indole 4-H), 7.31 (dt, $^4J$ = 0.9 Hz, $^3J$ = 7.9 Hz, 1H, indole 7-H), 7.15 (td, $^4J$ = 1.4 Hz, $^3J$ = 6.7 Hz, 1H, indole 6-H), 7.15-7.06 (m, 1H, indole 5-H), 6.12 (dd, $^3J$ = 17.7, 10.3 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.67 (s, br, 1H, $CH_2NH$CHO), 5.18 (dd, $^3J$ = 6.7 Hz, $^2J$ = 1.2 Hz, 1H, : $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.14 (s, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 3.54-3.46 (m, 2H, $CCH_2CH_2$NHCHO), 3.13-3.04 (m, 2H, $CCH_2CH_2$NHCHO), 1.53 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 164.3 (*C*HO), 145.9 ($C(CH_3)_2CH$=$CH_2$), 140.2 (indole C-2), 134.2 (indole C-7a), 129.6 (indole C-3a), 121.7 (indole C-6), 119.4 (indole C-5), 117.8 (indole C-4), 112.0 ($C(CH_3)_2CH$=$CH_2$), 110.7 (indole C-7), 106.6 (indole C-3), 42.1 ($CCH_2CH_2$NHCHO), 39.0 (NHC$C(CH_3)_2$CH), 28.1 (2C, $C(CH_3)_2CH$=$CH_2$), 25.3 ($CCH_2CH_2$NHCHO).

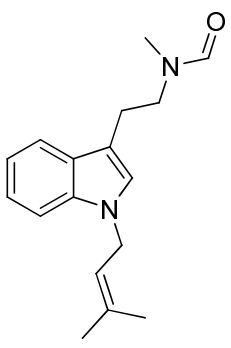
**IR** (ATR): $\tilde{\nu}$ = 3299 cm$^{-1}$ (w, br), 3056 (w), 2968 (w), 2868 (w), 1660 (s, br), 1517 (w), 1460 (m), 1435 (m), 1383 (m), 1338 (w), 1304 (w), 1238 (m, br), 1173 (w), 1006 (w), 915 (m), 741 (s, br).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 283 nm (3.79), 240 (3.88), 232 (3.69).

**MS** (EI, 70 eV): *m/z* (%) = 256 $[M]^+$ (27), 198 $[M\text{-}C_2H_4NO]^+$ (100), 184 $[M\text{-}C_3H_6NO]^+$ (9), 168 (48).

**GC-HRMS** (EI): calcd. for $C_{15}H_{20}N_2$ $[M]^+$ 256.1576,
found 256.1572.

### *N*-Methyl-*N*-(2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)formamide (146)



**146**

To NaH (60% in mineral oil, 713 mg, 17.81 mmol, 1.2 eq.) was added $N_b$-formyl-$N_b$-methyltryptamine (**131**, 3.0 g, 14.84 mmol, 1.0 eq.) dissolved in DMF (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Prenylbromide (2.1 mL, 17.81 mmol, 1.2 eq.) was added drop wise at 0 °C and the reaction mixture was allowed to warm to rt, stirred further for 3 h. $H_2O$ (25 mL) was cautiously added and the aqueous phase was extracted with $Et_2O$ (3 x 100

mL). The combined ethereal phases were washed with $H_2O$ (3 x 100 mL), brine (1 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc) to afford compound **146** (3.36 g, 12.14 mmol, 84%) as a red oil.

**TLC** [silica gel, EtOAc]: $R_f$ = 0.54.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.82 (s, 1H, C*H*O), 7.53 (d, $^3J$ = 7.9 Hz, 1 H, indole 7-H), 7.29 (d, $^3J$ = 8.2 Hz, 1 H, indole 4-H), 7.13-7.08 (m, 2H, indole 5-H, indole 6-H), 6.87 (s, 1H, indole 2-H), 5.36-5.31 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.63 (d, $^3J$ = 6.9 Hz, 2H, $NCH_2CH$=$C(Me)_2$), 3.51 (t, $^3J$ = 7.0 Hz, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.98 (t, $^3J$ = 7.0 Hz, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.91 (s, $NCH_3$), 1.81 (s, 6H, $NCH_2CH$=$C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 (*C*HO), 136.5 ($NCH_2CH$=*C*$(CH_3)_2$), 136.1 (indole C-7a), 127.6 (indole C-3a), 125.2 (indole C-2), 119.9 ($NCH_2CH$=$C(CH_3)_2$), 119.1, 118.9 (indole C-6, indole C-5), 118.4 (indole C-7), 110.3 (indole C-3), 109.8 (indole C-4), 50.3 ($CCH_2CH_2N(CH_3)CHO$), 44.0 ($NCH_2CH$=$C(CH_3)_2$), 29.7 ($N(CH_3)CHO$), 25.7 (2C, $NCH_2CH$=$C(CH_3)_2$), 24.6 ($CCH_2CH_2N(CH_3)CHO$).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.05 (s, 1H, C*H*O), 7.63 (d, $^3J$ = 7.9 Hz, 1 H, indole 7-H), 7.30 (d, $^3J$ = 8.2 Hz, 1 H, indole 4-H), 7.23-7.19 (m, 2H, indole 5-H, indole 6-H), 6.96 (s, 1H, indole 2-H), 5.36-5.31 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.63 (d, $^3J$ = 6.9 Hz, 2H, $NCH_2CH$=$C(Me)_2$), 3.63 (t, $^3J$ = 7.0 Hz, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.99 (t, $^3J$ = 7.0 Hz, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.88 (s, $NCH_3$), 1.76 (s, 6H, $NCH_2CH$=$C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.7 (*C*HO), 136.5 ($NCH_2CH$=*C*$(CH_3)_2$), 136.3 (CH=*C*$(CH_3)_2$),136.2 (indole C-7a), 128.0 (indole C-3a), 125.3 (indole C-2), 120.0 ($NCH_2CH$=$C(CH_3)_2$), 121.7, 121.5 (indole C-6, indole C-5), 118.8 (indole C-7), 111.3 (indole C-3), 119.6 (indole C-4), 45.2 ($CCH_2CH_2N(CH_3)CHO$), 43.9 ($NCH_2CH$=$C(CH_3)_2$), 35.0 ($N(CH_3)CHO$), 22.8 ($CCH_2CH_2N(CH_3)CHO$), 18.0 (2C, $NCH_2CH$=$C(CH_3)_2$).

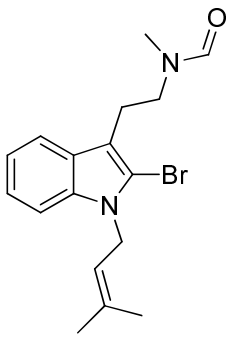
**IR** (ATR): $\tilde{\nu}$ = 3051 $cm^{-1}$ (w), 2967 (w), 2918 (w), 2858 (w), 1665 (s), 1465 (m), 1393 (m), 1333 (w), 1164 (w), 1069 (m), 1014 (w), 844 (w), 737 (s), 654 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 292 nm (3.75), 240 (3.99).

**MS** (EI, 70 eV): *m/z* (%) = 270 $[M]^+$ (23), 211 $[M\text{-}C_2H_4NO]^+$ (50), 198 $[M\text{-}C_3H_6NO]^+$ (33), 143 (33), 130 $[C_9H_9N]^+$ (100), 69 (26).

**HRMS** (EI): calcd. for $C_{17}H_{22}N_2O$ $[M]^+$ 270.1727,
found 270.1733.

### *N*-(2-(2-Bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)-*N*-methylformamide (167)



**167**

To a stirred solution of $N_a$-prenyl-$N_b$-formyl-$N_b$-methyltryptamine (**146**, 500 mg, 1.85 mmol, 1.0 eq.) in HOAc-$HCO_2H$ (16 mL, 3:1) was added a solution of NBS (336 mg, 1.89 mmol, 1.02 eq.) in HOAc-$HCO_2H$ (8 mL, 3:1). The solution was stirred at rt for 3 h, before the solution was added to a mixture of $Et_2O$ (70 mL) and ice (70 g) and was diluted with $Et_2O$ (100 mL). The organic layer was washed with $H_2O$ (3 x 50 mL) and with aqueous NaOH (1 M, 50 mL). The organic layer was washed again with $H_2O$ (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc/Hexane (1:1)) to afford the title compound **167** (148 mg, 0.43 mmol, 23%) as a black oil which degrades over time.

**TLC** [silica gel, EtOAc/Hexane (1:1)]: $R_f$ = 0.42.

Ratio of rotamers in $CDCl_3$: 1.0:0.5.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.76 (s, 1H, C*H*O), 7.46 (d, $^3J$ = 7.5 Hz, 1H, indole 7-H), 7.246 (d, $^3J$ = 4.3 Hz, 1H, indole 4-H), 7.21-7.16 (m, 1H, indole 5-H), 7.12 (dd, $^3J$ = 7.0 Hz, $^4J$ = 1.0 Hz, 1H, indole 6-H), 5.17-5.12 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.76 (d, $^3J$ = 6.5 Hz, 2H, $NCH_2CH$=$C(Me)_2$), 3.48 (t, $^3J$ = 6.9 Hz, 2H, $CCH_2CH_2N(CH_3)CHO$),

3.02-2.96 (m, 2H, CC*H*$_2$CH$_2$N(CH$_3$)CHO), 2.94 (s, 3H, CCH$_2$CH$_2$N(C*H*$_3$)CHO), 1.86 (s, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.70 (d, $^4J$ = 1.3 Hz, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 (*C*HO), 136.2 (indole C-7a), 135.1 (NCH$_2$CH=*C*(CH$_3$)$_2$), 126.9 (indole C-3a), 122.0 (indole C-5), 119.8, (indole C-6), 117.5 (indole C-7), 119.6 (NCH$_2$*C*H=C(CH$_3$)$_2$), 113.2 (indole C-2), 110.3 (indole C-3), 109.9 (indole C-4), 49.2 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 43.3 (N*C*H$_2$CH=C(CH$_3$)$_2$), 30.0 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 25.5 (2C, NCH$_2$CH=C(*C*H$_3$)$_2$), 24.8 (C*C*H$_2$CH$_2$N(CH$_3$)CHO).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.03 (s, 1H, C*H*O), 7.62 (d, $^3J$ = 7.8 Hz, 1H, indole 7-H), 7.253 (d, $^3J$ = 4.3 Hz, 1H, indole 4-H), 7.21-7.16 (m, 1H, indole 5-H), 7.10 (dd, $^3J$ = 7.0 Hz, $^4J$ = 1.0 Hz, indole 6-H), 5.17-5.12 (m, 1H, NCH$_2$C*H*=C(CH$_3$)$_2$), 4.76 (d, $^3J$ = 6.5 Hz, 2H, N*C*H$_2$CH=C(Me)$_2$), 3.55 (dd, $^3J$ = 6.8, 8.2 Hz, 2H, CCH$_2$C*H*$_2$N(CH$_3$)CHO), 3.02-2.96 (m, 2H, CC*H*$_2$CH$_2$N(CH$_3$)CHO), 2.84 (s, 3H, CCH$_2$CH$_2$N(C*H*$_3$)CHO), 1.86 (s, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.70 (d, $^4J$ = 1.3 Hz, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.5 (*C*HO), 136.1 (indole C-7a), 135.0 (NCH$_2$CH=*C*(CH$_3$)$_2$), 127.3 (indole C-3a), 122.0 (indole C-5), 119.7 (indole C-6), 118.2 (indole C-7), 119.6 (NCH$_2$*C*H=C(CH$_3$)$_2$), 112.7 (indole C-2), 111.5 (indole C-3), 109.6 (indole C-4), 44.5 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 43.2 (N*C*H$_2$CH=C(CH$_3$)$_2$), 35.2 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 23.1 (C*C*H$_2$CH$_2$N(CH$_3$)CHO), 18.2 (2C, NCH$_2$CH=C(*C*H$_3$)$_2$).

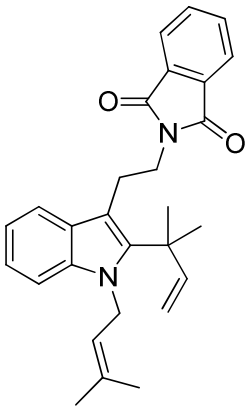
**IR** (ATR): $\tilde{\nu}$ = 3053 cm$^{-1}$ (w), 2968 (w), 2924 (w), 2857 (w), 1668 (s), 1453 (s), 1383 (m), 1352 (m), 1333 (m), 1311 (m), 1217 (w), 1179 (m), 1155 (w), 1069 (m), 1041 (w), 1014 (w), 843 (w), 738 (s), 567 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 354 nm (1.72), 286 (3.93), 240 (4.03), 231 (3.71).

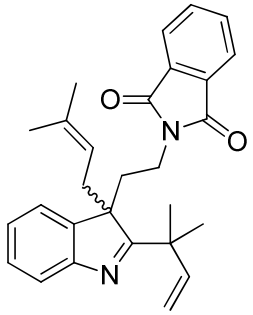
**MS** (EI, 70 eV): *m/z* (%) = 351 (3), 350 (15), 349 (3), 348 (16), 292 (5), 291 (26), 290 (5), 289 (27), 269 (21), 223 (5), 222 (31), 221 (5), 220 (32), 211 (11), 210 (99), 209 (12), 208 (100), 181 (5), 130 (9), 129 (15), 128 (17), 101 (9), 77 (6), 69 (44).

**HRMS** (EI): calcd. for $C_{17}H_{22}BrN_2O$ $[M]^+$ 348.0832,
found 348.0827.

**2-(2-(1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (168) and 2-(2-(3-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (169)**



**168**



**169**

To NaH (60% in mineral oil, 292 mg, 7.31 mmol, 5.0 eq.) was added pentane (4 mL) at rt and stirred for 2 min. Pentane was removed via syringe. The reaction flask was cooled on an ice bath and 2-*tert*-prenyl-phthaloyltryptamine (**166**, 524 mg, 1.46 mmol, 1.0 eq.) in DMF (30 mL) was added drop wise at 0 °C and the reaction mixture was stirred for 2 h at 0 °C. To the red colored reaction mixture, prenylchloride (0.72 mL, 5.84 mmol, 4.0 eq.) in DMF (2 mL) was added drop wise and stirred at rt for 24 h. $H_2O$ (50 mL) was cautiously added and the reaction mixture was extracted with TBME (4 x 70 mL). The combined etherial layers were washed with $H_2O$ (3 x 70 mL), brine (1 x 70 mL), dried over $Na_2SO_4$, and concentrated in vacuum. The residual oil was purified by column chromatography (silica gel, EtOAc/petrolether (4:1 to 1:1)) to obtain the title compounds **169** (383 mg, 0.9 mmol, 61%) and **168** (98 mg, 0.23 mmol, 16%) as pale yellow solids.

**TLC** [silica gel, EtOAc/petrolether (4:1)]: $R_f$ = 0.63.

**Mp**: 161-162 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.85 (dd, $^3J$ = 5.4, 3.1 Hz, 2H, N(C(=O)CC*H*CH)$_2$), 7.83-7.80 (m, 1H, indole 4-H), 7.71 (dd, $^3J$ = 5.4, 3.0 Hz, 2H, N(C(=O)CCHC*H*)$_2$), 7.15-7.10 (m, 3H, indole 5-H, indole 6-H, indole 7-H), 6.23 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $C(CH_3)_2C\mathit{H}=CH_2$), 5.15-5.12 (m, 1H, $NCH_2C\mathit{H}=C(CH_3)_2$), 5.09 (dd, $^3J$ = 10.6 Hz,

$^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 5.01 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 4.80 (d, $^3J$ = 5.5 Hz, 2H, $NCH_2CH=C(CH_3)_2$), 3.91-3.87 (m, 2H, $CCH_2CH_2N$(phthaloyl)), 3.35-3.31 (m, 2H, $CCH_2CH_2N$(phthaloyl)), 1.78 (d, $^4J$ = 0.9 Hz, 3H, $NCH_2CH=C(CH_3)_2$), 1.70 (s, 9H, $C(CH_3)_2CH=CH_2$, $NCH_2CH=C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.4 (2C, $N(C(=O)CCHCH)_2$), 145.6 ($C(CH_3)_2CH=CH_2$), 140.6 (indole C-2), 136.9 (indole C-7a), 133.8 (2C, $N(C(=O)CCHCH)_2$), 133.0 (2C, $N(C(=O)CCHCH)_2$), 132.3 ($NCH_2CH=C(CH_3)_2$), 128.9 (indole C-3a), 123.1 (2C, $N(C(=O)CCHCH)_2$), 122.2 ($NCH_2CH=C(CH_3)_2$), 121.5 (indole C-6), 119.2 (indole C-5), 118.2 (indole C-4), 111.8 ($C(CH_3)_2CH=CH_2$), 109.6 (indole C-7), 107.7 (indole C-3), 44.1 ($NCH_2CH=C(CH_3)_2$), 40.8 ($NCC(CH_3)_2CH=CH_2$), 39.4 ($CCH_2CH_2N$(phthaloyl)), 29.7 (2C, $NCC(CH_3)_2CH=CH_2$), 25.4 ($NCH_2CH=C(CH_3)_2$), 25.1 ($CCH_2CH_2N$(phthaloyl)), 18.3 ($NCH_2CH=C(CH_3)_2$).

**IR** (ATR): $\tilde{\nu}$ = 3050 cm$^{-1}$ (w), 2919 (w), 2867 (w), 1771 (w), 1703 (s), 1467 (w), 1429 (w), 1394 (m), 1352 (m), 1329 (w), 1255 (w), 1188 (w), 1103 (m), 1018 (m), 995 (w), 910 (w), 876 (w), 793 (w), 733 (s), 716 (s), 625 (w), 592 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 292 nm (3.94), 241 (4.27).

**MS** (EI, 70 eV): *m/z* (%) = 449 $[M+Na]^+$ (100), 427 $[M+H]^+$ (11).

**HRMS** (ESI): calcd. for $C_{28}H_{30}NaN_2O_2$ $[M+Na]^+$ 449.2199,

found 449.2203.

Compound **169**

**TLC** [silica gel, EtOAc/petrolether (4:1)]: $R_f$ = 0.42.

**Mp**: 143-146 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.76 (dd, $^3J$ = 5.5, 3.0 Hz, 2H, $N(C(=O)CCHCH)_2$), 7.67 (dd, $^3J$ = 5.5, 3.0 Hz, 2H, $N(C(=O)CCHCH)_2$), 7.57 (dd, $^4J$ = 1.3 Hz, $^3J$ = 7.3 Hz, 1H, indole 7-H), 7.27-7.25 (m, 2H, indole 6-H, indole 4-H), 7.20-7.17 (m, 1H, indole 5-H), 6.40 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.32 (dd, $^3J$ = 17.5 Hz, $^2J$ = 1.1 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.22 (dd, $^3J$ = 10.7 Hz, $^2J$ = 1.1 Hz, 1H,

$C(CH_3)_2CH=CH_2$-$H_Z$), 4.46-4.44 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 3.18 (ddd, $^3J$ = 11.8, 4.5 Hz, $^2J$ = 13.7 Hz, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.92 (ddd, $^3J$ = 11.3, 5.6 Hz, $^2J$ = 13.7 Hz, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.69 (dd, $^3J$ = 6.2 Hz, $^2J$ = 15.0 Hz, 1H, $CCH_2CH_2N$(phthaloyl)), 2.57 (dd, $^3J$ = 5.8 Hz, $^2J$ = 14.6 Hz, 1H, $CCH_2CH_2N$(phthaloyl)), 2.53 (ddd, $^3J$ = 11.3, 4.5 Hz, $^2J$ = 13.4 Hz, 1H, $CCH_2CH_2N$(phthaloyl)), 2.35 (ddd, $^3J$ = 11.8, 5.6 Hz, $^2J$ = 13.4 Hz, 1H, $CCH_2CH_2N$(phthaloyl)), 1.68 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.56 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.51 (d, $^4J$ = 1.1 Hz, 3H, $N=CCCH_2CH=C(CH_3)_2$), 1.46 (s, 3H, $N=CCCH_2CH=C(CH_3)_2$.

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 190.7 (indole C-2), 167.9 (2C, $N(C(=O)CCHCH)_2$), 153.7 (indole C-7a), 144.5 ($C(CH_3)_2CH=CH_2$), 141.6 (indole C-3a), 134.3 ($N=CCCH_2CH=C(CH_3)_2$), 133.8 (2C, $N(C(=O)CCHCH)_2$), 132.0 (2C, $N(C(=O)CCHCH)_2$), 127.8 (indole C-6), 125.7 (indole C-5), 123.0 (2C, $N(C(=O)CCHCH)_2$), 121.5 (indole C-4), 120.1 (indole C-7), 118.2 ($N=CCCH_2CH=C(CH_3)_2$), 113.1 ($C(CH_3)_2CH=CH_2$), 62.8 (indole C-3), 43.7 ($N=CC(CH_3)_2CH=CH_2$), 35.3 ($CCH_2CH_2N$(phthaloyl)), 34.1 ($CCH_2CH_2N$(phthaloyl)), 34.0 ($N=CCCH_2CH=C(CH_3)_2$), 27.6 ($N=CC(CH_3)_2CH=CH_2$), 27.5 ($N=CC(CH_3)_2CH=CH_2$), 25.6 ($N=CCCH_2CH=C(CH_3)_2$), 18.2 ($N=CCCH_2CH=C(CH_3)_2$).

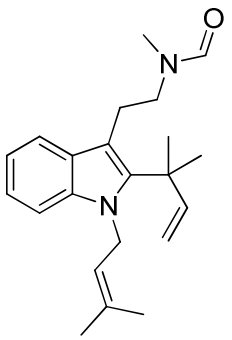
**IR** (ATR): $\tilde{\nu}$ = 2970 cm$^{-1}$ (w), 2929 (w), 2877 (w), 1717 (s), 1636 (s), 1540 (w), 1491 (w), 1451 (m), 1376 (m), 1261 (s), 1123 (m), 1075 (m), 1039 (w), 917 (w), 840 (w), 749 (s), 708 (m), 678 (w), 645 (w), 577 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 240 nm (3.93).

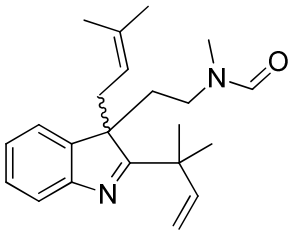
**MS** (EI, 70 eV): *m/z* (%) = 449 $[M+Na]^+$ (5).

**HRMS** (ESI): calcd. for $C_{28}H_{30}NaN_2O_2$ $[M+Na]^+$ 449.2199,
found 449.2201.

***N*-Methyl-*N*-(2-(1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)formamide (27) and *N*-methyl-*N*-(2-(3-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)ethyl)formamide (174):**



**27**



**174**

To NaH (60% in mineral oil, 740 mg, 18.51 mmol, 5.0 eq.) was added pentane (3 mL) at rt and stirred for 2 min. Pentane was removed via syringe. The reaction mixture was cooled on an ice bath and debromoflustrabromine (**2**, 1.0 g, 3.70 mmol, 1.0 eq.) in DMF (23 mL) was added drop wise and stirred for 2 h at 0 °C. Prenylchloride (1.73 mL, 14.81 mmol, 4.0 eq.) in DMF (2 mL) was added drop wise to the reaction mixture and stirred at 0 °C for 6 h. $H_2O$ (50 mL) was cautiously added and the reaction mixture was extracted with TBME (4 x 150 mL). The combined etherial layers were washed with $H_2O$ (3 x 150 mL), brine (150 mL), dried over $Na_2SO_4$, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc/petrolether (4:1 to 1:1)) to obtain the title compounds **27** (467 mg, 1.41 mmol, 37%) and **174** (648 mg, 1.96 mmol, 52%) as pale yellow oils.

**TLC** [silica gel, EtOAc/petrolether (4:1)]: $R_f$ = 0.41.

Ratio of rotamers in $CDCl_3$: 1:0.7.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.04 (s, $CCH_2CH_2N(CH_3)CHO$), 7.47 (d, $^4J$ = 1.0 Hz, $^3J$ = 7.7 Hz, 1H, indole 4-H), 7.20-7.14 (m, 2H, indole 5-H, indole 6-H), 7.13-7.09 (m, 1H, indole 7-H), 6.18 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.13-5.11 (m, 1H, $NCH_2CH=C(CH_3)_2$), 5.09 (d, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.97 (dt, $^3J$ = 17.5 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 4.80-4.78 (m, 2H,

NC*H*$_2$CH=C(CH$_3$)$_2$), 3.45-3.41 (m, 2H, CC*H*$_2$CH$_2$N(CH$_3$)CHO), 3.24-3.19 (m, 2H, CCH$_2$C*H*$_2$N(CH$_3$)CHO), 2.99 (s, 3H, CCH$_2$CH$_2$N(C*H*$_3$)CHO), 1.70 (d, $^4J$ = 1.3 Hz, 6H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.60 (s, 6H, NCC(C*H*$_3$)$_2$CH=CH$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ = 162.5 (CH$_2$CH$_2$N(CH$_3$)*C*HO), 147.6 (C(CH$_3$)$_2$*C*H=CH$_2$), 140.5 (indole C-2), 137.0 (indole C-7a), 133.3 (NCH$_2$CH=*C*(CH$_3$)$_2$), 128.4 (indole C-3a), 121.9 (NCH$_2$*C*H=C(CH$_3$)$_2$), 121.5 (indole C-5), 119.2 (indole C-7), 117.4 (indole C-4), 111.7 (C(CH$_3$)$_2$CH=*C*H$_2$), 109.9 (indole C-5), 107.4 (indole C-3), 51.3 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 44.2 (N*C*H$_2$CH=C(CH$_3$)$_2$), 40.8 (NC*C*(CH$_3$)$_2$CH=CH$_2$), 30.0 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 29.7 (2C, CC(*C*H$_3$)$_2$CH=CH$_2$), 25.6 (C*C*H$_2$CH$_2$N(CH$_3$)CHO), 25.4 (2C, NCH$_2$CH=C(*C*H$_3$)$_2$).

Minor Rotamer:

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ = 8.06 (s, CCH$_2$CH$_2$N(CH$_3$)C*H*O), 7.64 (dt, $^3J$ = 7.5, 4.1 Hz, 1H, indole 4-H), 7.20-7.14 (m, 2H, indole 5-H, indole 6-H), 7.13-7.09 (m, 1H, indole 7-H), 6.19 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, C(CH$_3$)$_2$C*H*=CH$_2$), 5.13-5.11 (m, 1H, NCH$_2$C*H*=C(CH$_3$)$_2$), 5.07 (d, $^3J$ = 10.6 Hz, $^2J$ = 1.0 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_Z$), 4.97 (dt, $^3J$ = 17.5 Hz, $^2J$ = 0.8 Hz, 1H, C(CH$_3$)$_2$CH=C*H*$_2$-H$_E$), 4.80-4.78 (m, 2H, NC*H*$_2$CH=C(CH$_3$)$_2$), 3.53-3.49 (m, 2H, CC*H*$_2$CH$_2$N(CH$_3$)CHO), 3.24-3.19 (m, 2H, CCH$_2$C*H*$_2$N(CH$_3$)CHO), 2.96 (s, 3H, CH$_2$CH$_2$N(C*H*$_3$)CHO), 1.78 (s, 6H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.65 (s, 6H, NCC(C*H*$_3$)$_2$CH=CH$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ = 162.4 (CH$_2$CH$_2$N(CH$_3$)*C*HO), 147.9 (C(CH$_3$)$_2$*C*H=CH$_2$), 140.4 (indole C-2), 136.9 (indole C-7a), 133.1 (NCH$_2$CH=*C*(CH$_3$)$_2$), 128.8 (indole C-3a), 122.1 (NCH$_2$*C*H=C(CH$_3$)$_2$), 121.7 (indole C-5), 119.1 (indole C-7), 117.9 (indole C-4), 112.0 (C(CH$_3$)$_2$CH=*C*H$_2$), 109.6 (indole C-5), 108.2 (indole C-3), 46.6 (CCH$_2$*C*H$_2$N(CH$_3$)CHO), 44.1 (N*C*H$_2$CH=C(CH$_3$)$_2$), 40.8 (NC*C*(CH$_3$)$_2$CH=CH$_2$), 35.1 (CCH$_2$CH$_2$N(*C*H$_3$)CHO), 29.7 (2C, CC(*C*H$_3$)$_2$CH=CH$_2$), 23.1 (C*C*H$_2$CH$_2$N(CH$_3$)CHO), 18.3 (2C, NCH$_2$CH=C(*C*H$_3$)$_2$).

**IR** (ATR): $\tilde{\nu}$ = 2968 cm$^{-1}$ (w), 2927 (m), 2866 (w), 1668 (s), 1470 (m), 1451 (m), 1396 (w), 1350 (w), 1312 (w), 1241 (w), 1177 (m), 1066 (m), 1040 (w), 1006 (w), 910 (m), 840 (w), 744 (s), 697 (w), 578 (m).

**UV** (CHCl$_3$): $\lambda_{max}$ (log ε) = 290 nm (3.84), 240 (4.09).

**MS** (ESI): *m/z* (%) = 361 $[M+Na]^+$ (100), 339 $[M+H]^+$ (6).

| | | |
|---|---|---|
| **HRMS** (ESI): | calcd. for $C_{22}H_{31}N_2O$ $[M+H]^+$ | 339.2431, |
| | found | 339.2433. |

**Compound 174:**

**TLC** [silica gel, EtOAc/petrolether (2:1)]: $R_f$ = 0.22.

Ratio of rotamers in $CDCl_3$: 1:0.6.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.64(s, $CCH_2CH_2N(CH_3)CHO$), 7.59 (d, $^3J$ = 7.0 Hz, 1H, indole 7-H), 7.33 (dt, $^4J$ = 1.2 Hz, $^3J$ = 7.3 Hz, 1H, indole 6-H), 7.20 (dd, $^4J$ = 1.0 Hz, $^3J$ = 6.2 Hz, 1H, indole 5-H), 7.14 (d, $^3J$ = 7.4 Hz, 1 H, indole 4-H), 6.25 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $N=CC(CH_3)_2CH=CH_2$), 5.27 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.20 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.43-4.37 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.75-2.71 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.70 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 2.69-2.65 (m, 2H, $N=CCCH_2CH=C(CH_3)_2$), 2.42 (ddd, $^3J$ = 12.9, 4.6 Hz, $^2J$ = 11.3 Hz, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.32-2.20 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.14-2.06 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 1.55 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.53 (s, 6H, $N=CCCH_2CH=C(CH_3)_2$, $N=CC(CH_3)_2CH=CH_2$), 1.50 (s, 3H, $N=CCCH_2CH=C(CH_3)_2$.

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 190.1 (indole C-2), 162.2 ($CH_2CH_2N(CH_3)CHO$), 153.7 (indole C-7a), 144.6 ($C(CH_3)_2CH=CH_2$), 141.7 (indole C-3a), 134.6 ($N=CCCH_2CH=C(CH_3)_2$), 128.1 (indole C-6), 125.8 (indole C-5), 120.9 (indole C-4), 120.4 (indole C-7), 117.8 ($CCH_2CH=C(CH_3)_2$), 113.0 ($C(CH_3)_2CH=CH_2$), 62.6 (indole C-3), 45.0 ($CCH_2CH_2N(CH_3)CHO$), 43.7 ($N=CC(CH_3)_2CH=CH_2$), 35.5 ($N=CCCH_2CH=C(CH_3)_2$), 35.0 ($CCH_2CH_2N(CH_3)CHO$), 34.5 ($CCH_2CH_2N(CH_3)CHO$), 27.9 ($N=CC(CH_3)_2CH=CH_2$), 26.9 ($N=CC(CH_3)_2CH=CH_2$), 25.5 ($N=CCCH_2CH=C(CH_3)_2$), 18.2 ($N=CCCH_2CH=C(CH_3)_2$).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.87 (s, $CCH_2CH_2N(CH_3)CHO$), 7.58 (d, $^3J$ = 6.2 Hz, 1H, indole 7-H), 7.32-7.29 (m, 1H, indole 6-H), 7.23 (dd, $^4J$ = 1.1 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 7.22 (dd, $^4J$ = 1.0 Hz, $^3J$ = 4.3 Hz, 1H, indole 4-H), 6.34 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $N=CC(CH_3)_2CH=CH_2$), 5.27 (dd, $^3J$ = 17.5 Hz, $^2J$ = 1.3 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.19 (dd, $^3J$ = 10.6 Hz, $^2J$ = 1.0 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.43-4.37 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 3.00 (ddd, $^3J$ = 13.0, 4.9 Hz, $^2J$ = 11.8 Hz, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.67 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 2.64-2.58 (m, 2H, $N=CCCH_2CH=C(CH_3)_2$), 2.41 (ddd, $^3J$ = 12.9, 4.8 Hz, $^2J$ = 11.5 Hz, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.32-2.20 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.14-2.06 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 1.60 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.51 (s, 6H, $N=CCCH_2CH=C(CH_3)_2$, $N=CC(CH_3)_2CH=CH_2$), 1.48 (s, 3H, $N=CCCH_2CH=C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 190.1 (indole C-2), 162.2 ($CH_2CH_2N(CH_3)CHO$), 153.7 (indole C-7a), 144.6 ($C(CH_3)_2CH=CH_2$), 142.0 (indole C-3a), 134.2 ($N=CCCH_2CH=C(CH_3)_2$), 127.8 (indole C-6), 125.6 (indole C-5), 121.2 (indole C-4), 120.1 (indole C-7), 118.2 ($CCH_2CH=C(CH_3)_2$), 112.8 ($C(CH_3)_2CH=CH_2$), 62.8 (indole C-3), 43.7 ($N=CC(CH_3)_2CH=CH_2$), 40.6 ($CCH_2CH_2N(CH_3)CHO$), 35.2 ($N=CCCH_2CH=C(CH_3)_2$), 34.5 ($CCH_2CH_2N(CH_3)CHO$), 32.8 ($CCH_2CH_2N(CH_3)CHO$), 27.8 ($N=CC(CH_3)_2CH=CH_2$), 27.2 ($N=CC(CH_3)_2CH=CH_2$), 25.5 ($N=CCCH_2CH=C(CH_3)_2$), 18.2 ($N=CCCH_2CH=C(CH_3)_2$).

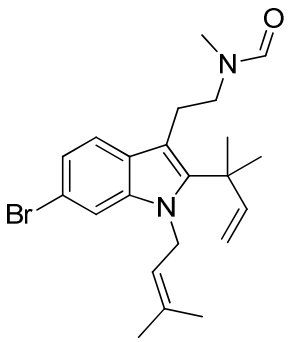
**IR** (ATR): $\tilde{\nu}$ = 2968 $cm^{-1}$ (w), 2925 (w), 2863 (w), 1674 (s), 1540 (w), 1455 (m), 1381 (m), 1298 (w), 1240 (w), 1118 (w), 1075 (w), 1011 (w), 918 (w), 835 (w), 762 (m), 739 (w), 685 (w), 586 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 264 nm (3.83), 238 (3.75).

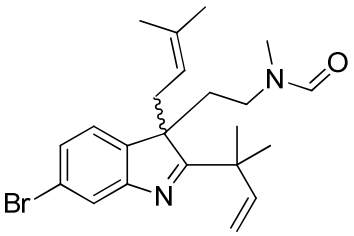
**MS** (ESI): *m/z* (%) = 361 $[M+Na]^+$ (100), 339 $[M+H]^+$ (15).

| | | |
|---|---|---|
| **HRMS** (ESI): | calcd. for $C_{22}H_{31}N_2O$ $[M+H]^+$ | 339.2431, |
| | found | 339.2433. |

***N*-(2-(6-Bromo-1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl) ethyl)-*N*-methylformamide (175) and *N*-(2-(6-bromo-3-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)ethyl)-*N*-methylformamide (176):**




**175**




**176**

To NaH (60% in mineral oil, 574 mg, 14.36 mmol, 5.0 eq.) was added pentane (3 mL) at rt and stirred for 2 min. Pentane was removed via syringe. The reaction mixture was cooled on an ice bath and flustrabromine (**1**, 1.0 g, 2.87 mmol, 1.0 eq.) in DMF (30 mL) was added drop wise and stirred for 2 h at 0 °C. Prenylchloride (1.35 mL, 11.49 mmol, 4.0 eq.) in DMF (2 mL) was added drop wise to the reaction mixture and stirred for 24 h. $H_2O$ (50 mL) was cautiously added and the reaction mixture was extracted with TBME (4 x 150 mL). The combined ethereal layers were washed with $H_2O$ (3 x 150 mL), brine (150 mL), dried over $Na_2SO_4$ and concentrated in vacuum. The crude residue was chromatographed over RP-18 silica gel (MeOH/$H_2O$ (5:1)) to obtain the title compounds **175** (488 mg, 1.17 mmol, 41%) and **176** (592 mg, 1.43 mmol, 50%) as pale yellow oils.

**TLC** [RP-18 silica gel, MeOH/$H_2O$ (10:1)]: $R_f$ = 0.26.

Ratio of rotamers in $CDCl_3$: 1:0.9.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.00 (s, $CCH_2CH_2N(CH_3)CHO$), 7.31 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.29 (d, $^4J$ = 1.5 Hz, 1 H, indole 7-H), 7.20 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.3 Hz, 1H, indole 5-H), 6.16 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.11 (d, $^3J$ = 0.7 Hz, 1H, $NCH_2CH=C(CH_3)_2$), 5.07 (d, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.96 (dd, $^3J$ = 17.5 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 4.74 (d, $^3J$ = 4.2 Hz, 2H, $NCH_2CH=C(CH_3)_2$), 3.42-3.38 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 3.20-3.15 (m, 2H,

$CCH_2CH_2N(CH_3)CHO$), 2.96 (s, 3H, $CH_2CH_2N(CH_3)CHO$), 1.77 (s, 6H, $NCH_2CH=C(CH_3)_2$), 1.59 (s, 6H, $NCC(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 ($CH_2CH_2N(CH_3)CHO$), 147.3 ($C(CH_3)_2CH=CH_2$), 141.3 (indole C-2), 137.9 (indole C-7a), 134.0 ($NCH_2CH=C(CH_3)_2$), 127.3 (indole C-3a), 122.4 (indole C-5), 121.2 ($NCH_2CH=C(CH_3)_2$), 118.6 (indole C-4), 115.4 (indole C-6), 112.9 (indole C-7), 112.2 ($C(CH_3)_2CH=CH_2$), 107.8 (indole C-3), 51.3 ($CCH_2CH_2N(CH_3)CHO$), 44.3 ($NCH_2CH=C(CH_3)_2$), 40.78 ($NCC(CH_3)_2CH=CH_2$), 30.1 ($CCH_2CH_2N(CH_3)CHO$), 29.6 (2C, $CC(CH_3)_2CH=CH_2$), 25.4 (2C, $NCH_2CH=C(CH_3)_2$), 25.4 ($CCH_2CH_2N(CH_3)CHO$).

Minor Rotamer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.05 (s, $CCH_2CH_2N(CH_3)CHO$), 7.50 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.27 (d, $^4J$ = 1.6 Hz, 1 H, indole 7-H), 7.19 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.4 Hz, 1H, indole 5-H), 6.17 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $C(CH_3)_2CH=CH_2$), 5.09 (d, $^3J$ = 0.9 Hz, 1H, $NCH_2CH=C(CH_3)_2$), 5.085 (d, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.93 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 4.74 (d, $^3J$ = 4.2 Hz, 2H, $NCH_2CH=C(CH_3)_2$), 3.49-3.45 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 3.20-3.15 (m, 2H, $CCH_2CH_2N(CH_3)CHO$), 2.93 (s, 3H, $CH_2CH_2N(CH_3)CHO$), 1.72 (d, $^4J$ = 1.2 Hz, 6H, $NCH_2CH=C(CH_3)_2$), 1.64 (s, 6H, $NCC(CH_3)_2CH=CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 162.4 ($CH_2CH_2N(CH_3)CHO$), 147.6 ($C(CH_3)_2CH=CH_2$), 140.1 (indole C-2), 137.8 (indole C-7a), 133.8 ($NCH_2CH=C(CH_3)_2$), 127.7 (indole C-3a), 122.2 (indole C-5), 121.4 ($NCH_2CH=C(CH_3)_2$), 119.3 (indole C-4), 115.2 (indole C-6), 112.6 (indole C-7), 112.0 ($C(CH_3)_2CH=CH_2$), 108.6 (indole C-3), 46.6 ($CCH_2CH_2N(CH_3)CHO$), 44.2 ($NCH_2CH=C(CH_3)_2$), 40.83 ($NCC(CH_3)_2CH=CH_2$), 35.1 ($CCH_2CH_2N(CH_3)CHO$), 29.6 (2C, $CC(CH_3)_2CH=CH_2$), 23.1 ($CCH_2CH_2N(CH_3)CHO$), 18.3 (2C, $NCH_2CH=C(CH_3)_2$).

**IR** (ATR): $\tilde{\nu}$ = 2971 cm$^{-1}$ (w), 2927 (w), 2871 (w), 1726 (w), 1672 (s), 1600 (w), 1469 (m), 1384 (m), 1311 (w), 1244 (m), 1175 (w), 1061 (w), 998 (w), 914 (m), 850 (m), 802 (m), 597 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 302 nm (3.87), 394 (3.88), 242 (4.37).

**MS** (EI, 70 eV): *m/z* (%) = 421 (8), 420 (22), 419 (7), 418 (20), 346 (50), 344 (53), 279 (18), 278 (93), 277 (17), 276 (100), 263 (19), 261 (19), 167 (15), 69 (100).

| | | |
|---|---|---|
| **GC-HRMS** (EI): | calcd. for $C_{22}H_{29}BrN_2O$ $[M]^+$ | 416.1458, |
| | found | 416.1426. |

**Compound 176**

**TLC** [RP-18 silica gel, MeOH/$H_2O$ (5:1)]: $R_f$ = 0.23.

Ratio of rotamers in $CDCl_3$: 1:0.8.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.74 (d, $^4J$ = 1.8 Hz, 1H, indole 7-H), 7.70(s, $CCH_2CH_2N(CH_3)CHO$), 7.36 (dd, $^4J$ = 1.8 Hz, $^3J$ = 6.1 Hz, 1H, indole 5-H), 7.01 (d, $^3J$ = 7.9 Hz, 1 H, indole 4-H), 6.22 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, $N=CC(CH_3)_2CH=CH_2$), 5.27 (dd, $^3J$ = 17.5 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.21 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.6 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.42-4.36 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.98-2.91 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.70 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 2.67 (d, $^3J$ = 4.7 Hz, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.601 (d, $^3J$ = 7.2 Hz, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.45-2.36 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.33.2.25 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.11-2.03 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 1.53 (s, 6H, $N=CCCH_2CH=C(CH_3)_2$, $N=CC(CH_3)_2CH=CH_2$), 1.51 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.49 (s, 3H, $N=CCCH_2CH=C(CH_3)_2$.

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 192.1 (indole C-2), 162.1 ($CH_2CH_2N(CH_3)CHO$), 155.1 (indole C-7a), 144.2 ($C(CH_3)_2CH=CH_2$), 140.7 (indole C-3a), 135.2 ($N=CCCH_2CH=C(CH_3)_2$), 128.6 (indole C-5), 124.0 (indole C-7), 122.1 (indole C-4), 121.4 (indole C-6), 117.4 ($CCH_2CH=C(CH_3)_2$), 113.4 ($C(CH_3)_2CH=CH_2$), 62.6 (indole C-3), 44.9 ($CCH_2CH_2N(CH_3)CHO$), 43.9 ($N=CC(CH_3)_2CH=CH_2$), 35.3 ($N=CCCH_2CH=C(CH_3)_2$), 34.9 ($CCH_2CH_2N(CH_3)CHO$), 34.6 ($CCH_2CH_2N(CH_3)CHO$), 27.9 ($N=CC(CH_3)_2CH=CH_2$), 27.2 ($N=CC(CH_3)_2CH=CH_2$), 25.6 ($N=CCCH_2CH=C(CH_3)_2$), 18.3 ($N=CCCH_2CH=C(CH_3)_2$).

Minor Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.89 (s, $CCH_2CH_2N(CH_3)CHO$), 7.72 (d, $^4J$ = 1.4 Hz, 1H, indole 7-H), 7.34 (dd, $^4J$ = 1.4 Hz, $^3J$ = 5.8 Hz, 1H, indole 5-H), 7.07 (d, $^3J$ = 7.8 Hz, 1 H, indole 4-H), 6.31 (dd, $^3J$ = 17.4, 10.6 Hz, 1H, $N=CC(CH_3)_2CH=CH_2$), 5.27 (dd, $^3J$ = 17.5 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_E$), 5.20 (dd, $^3J$ = 10.7 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH=CH_2$-$H_Z$), 4.42-4.36 (m, 1H, $N=CCCH_2CH=C(CH_3)_2$), 2.76-2.73 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.71 (s, 3H, $CCH_2CH_2N(CH_3)CHO$), 2.64 (d, $^3J$ = 7.2 Hz, 2H, $N=CCCH_2CH=C(CH_3)_2$), 2.45-2.36 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.33-2.25 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 2.11-2.03 (m, 1H, $CCH_2CH_2N(CH_3)CHO$), 1.58 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.54 (d, $^4J$ = 1.4 Hz, 3H, $N=CCCH_2CH=C(CH_3)_2$), 1.49 (s, 3H, $N=CC(CH_3)_2CH=CH_2$), 1.47 (s, 3H, $N=CCCH_2CH=C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 192.9 (indole C-2), 162.2 ($CH_2CH_2N(CH_3)CHO$), 155.2 (indole C-7a), 144.3 ($C(CH_3)_2CH=CH_2$), 141.0 (indole C-3a), 134.8 ($N=CCCH_2CH=C(CH_3)_2$), 128.4 (indole C-5), 123.7 (indole C-7), 122.4 (indole C-4), 121.1 (indole C-6), 117.8 ($CCH_2CH=C(CH_3)_2$), 113.1 ($C(CH_3)_2CH=CH_2$), 62.9 (indole C-3), 43.9 ($N=CC(CH_3)_2CH=CH_2$), 40.5 ($CCH_2CH_2N(CH_3)CHO$), 35.1 ($N=CCCH_2CH=C(CH_3)_2$), 32.5 ($CCH_2CH_2N(CH_3)CHO$), 29.6 ($CCH_2CH_2N(CH_3)CHO$), 27.7 ($N=CC(CH_3)_2CH=CH_2$), 26.9 ($N=CC(CH_3)_2CH=CH_2$), 25.6 ($N=CCCH_2CH=C(CH_3)_2$), 18.2 ($N=CCCH_2CH=C(CH_3)_2$).

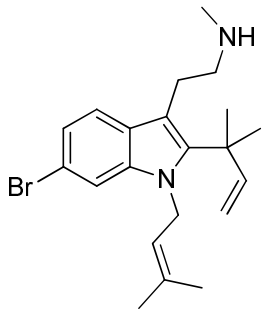
**IR** (ATR): $\tilde{\nu}$ = 2969 (w), 2926 (w), 2862 (w), 1672 (s), 1599 (w), 1538 (w), 1453 (m), 1380 (m), 1250 (w), 1106 (w), 1075 (m), 1009 (w), 919 (m), 894 (w), 873 (w), 817 (w), 754 (w), 691 (w), 596 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 267 nm (3.79), 240 (4.06).

**MS** (EI, 70 eV): *m/z* (%) = 442 (21), 441 (90), 440 (21), 439 (93), 419 (26), 417 (27), 351 (10), 349 (11), 257 (26)

| | | |
|---|---|---|
| **HRMS** (EI): | calcd. for $C_{22}H_{30}BrN_2O$ $[M+H]^+$ | 417.1536, |
| | found | 417.1538. |

**2-(6-Bromo-1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)-*N*-methylethanamine (24)**




**24**

To a solution of $N_a$-prenylflustrabromine (**175**, 150 mg, 0.36 mmol, 1.0 eq.) in EtOH (20 mL) was added 32% aq. NaOH (2 mL) at rt. The reaction mixture was refluxed for 48 h and cooled to rt. $H_2O$ (50 mL) was added and the reaction mixture was extracted with $Et_2O$ (3 x 80 mL), washed with $H_2O$ (4 x 50 mL), brine (50 mL), dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure affording the title compound **24** (128 mg, 0.33 mmol, 92 %) as a slight yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.43 (d, $^3J$ = 8.4 Hz, 1H, indole 4-H), 7.26 (d, $^4J$ = 2.2 Hz, 1 H, indole 7-H), 7.16 (dd, $^4J$ = 1.7 Hz, $^3J$ = 8.4 Hz, 1H, indole 5-H), 6.15 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.07 (d, $^3J$ = 0.9 Hz, 1H, $NCH_2CH$=$C(CH_3)_2$), 5.03 (d, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 4.93 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.72 (d, $^3J$ = 5.4 Hz, 2H, $NCH_2CH$=$C(CH_3)_2$), 3.14 (t, $^3J$ = 8.2 Hz, 2H, $CCH_2CH_2NHCH_3$), 2.79 (t, $^3J$ = 8.2 Hz, 2H, $CCH_2CH_2NHCH_3$), 2.46 (s, 3H, $CH_2CH_2NHCH_3$), 1.76 (d, $^4J$ = 0.9 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.71 (d, $^4J$ = 1.4 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.60 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 147.7 ($C(CH_3)_2CH$=$CH_2$), 140.7 (indole C-2), 137.7 (indole C-7a), 133.6 ($NCH_2CH$=$C(CH_3)_2$), 127.9 (indole C-3a), 121.9 (indole C-5), 121.6 ($NCH_2CH$=$C(CH_3)_2$), 119.4 (indole C-4), 115.0 (indole C-6), 112.5 (indole C-7), 111.9 ($C(CH_3)_2CH$=$CH_2$), 109.8 (indole C-3), 54.2 ($CCH_2CH_2NHCH_3$), 44.2 ($NCH_2CH$=$C(CH_3)_2$), 40.8 ($NC(CH_3)_2CH$=$CH_2$), 36.5 ($CCH_2CH_2NHCH_3$)), 29.7 (2C, $NCC(CH_3)_2CH$=$CH_2$), 25.8 ($CCH_2CH_2NHCH_3$), 25.4 ($NCH_2CH$=$C(CH_3)_2$), 18.3 ($NCH_2CH$=$C(CH_3)_2$).

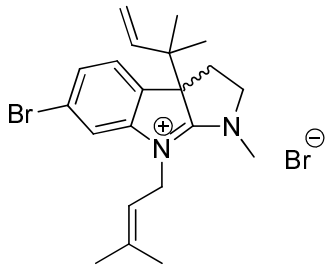
**IR** (ATR): $\tilde{\nu}$ = 3402 cm$^{-1}$ (w), 3310 (w), 3079 (w), 2969 (m), 2929 (m), 2875 (m), 2791 (w), 1598 (m), 1469 (s), 1447 (s), 1377 (m), 1311 (m), 1243 (w), 1117 (m), 1054 (m), 1037 (m), 1008 (m), 912 (s), 838 (m), 799 (s), 779 (m), 686 (w), 628 (w), 595 (m).

**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 351 nm (2.32), 300 (3.72), 293 (3.72), 234 (4.37), 191 (4.47).

**MS** (EI, 70 eV): *m/z* (%) = 391 (3), 390 (14), 389 (4), 388 (15), 348 (16), 348 (100), 346 (29), 345 (94), 344 (16), 279 (75), 278 (88), 277 (78), 276 (82), 264 (25), 262 (38), 69 (94).

| | | |
|---|---|---|
| **HRMS** (EI): | calcd. for $C_{21}H_{29}BrN_2$ $[M]^+$ | 388.1509, |
| | found | 388.1504. |

**6-Bromo-1-methyl-8-(3-methylbut-2-enyl)-3*a*-(2-methylbut-3-en-2-yl)-1,2,3,3*a*-tetrahydropyrrolo[2,3-*b*]indol-8-ium bromide (25)**




**25**

To a solution of $N_a$-prenyl-deformylflustrabromine (**24**, 46 mg, 0.12 mmol, 1.0 eq.) in THF (10 mL) was added NBS (24 mg, 0.13 eq. 1.1 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 12 h and concentrated in vacuum. The crude residue was purified by HPLC (RP-silica gel, MeOH/$H_2O$ (5:1)) to afford the title compound **25** (14 mg, 0.03 mmol, 26%) as a yellow oil.

**$^1$H NMR** (400 MHz, $D_2O$): $\delta$ = 7.29 (dd, $^4J$ = 1.6 Hz, $^3J$ = 8.0 Hz, 1H, 5-H), 7.09 (d, $^3J$ = 8.0 Hz, 1H, 4-H), 7.03 (d, $^4J$ = 1.6 Hz, 1H, 7-H), 6.02 (dd, $^3J$ = 17.4, 10.7 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.23-5.21 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 5.20 (d, $^3J$ = 10.7 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 5.14 (d, $^3J$ = 17.4 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 5.11-5.051 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.78 (dd, $^3J$ = 5.5 Hz, $^2J$ = 16.9 Hz, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.45-4.38 (m, 1H, =$CN(CH_3)NCH_2CH_2C$), 4.33 (t, $^2J$ = 10.5, 1H, =$CN(CH_3)CH_2CH_2C$), 3.77 (s, 3H, $N^+$=$CN(CH_3)CH_2CH_2C$), 2.69-2.61 (m, 1H, =$CN(CH_3)CH_2CH_2C$), 2.55 (dd, $^3J$ = 5.9 Hz, $^2J$ = 13.1 Hz, 1H, =$CN(CH_3)CH_2CH_2C$), 1.86 (s, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.80 (s, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.11 (s, 3H, N=$CCC(CH_3)_2CH$=$CH_2$), 1.0 (s, 3H, N=$CCC(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $D_2O$): $\delta$ = 180.0 (C-8a), 149.2 (C-7a), 141.1 ($C(CH_3)_2CH$=$CH_2$), 139.4 ($N^+CH_2CH$=$C(CH_3)_2$), 130.1 (C-3b), 126.9 (C-5), 125.9 (C-4), 122.9 (C-6), 116.9 ($N^+CH_2CH$=$C(CH_3)_2$), 116.2 ($C(CH_3)_2CH$=$CH_2$), 114.0 (C-7), 68.8 (C-3a), 65.7 (C-2), 46.2 ($N^+$=$CCC(CH_3)_2CH$=$CH_2$), 44.3 ($N^+CH_2CH$=$C(CH_3)_2$), 36.8 ($N^+$=$CN(CH_3)CH_2CH_2C$), 27.2 ($N^+$=$CN(CH_3)CH_2CH_2C$), 25.7 ($N^+CH_2CH$=$C(CH_3)_2$), 22.7 ($C(CH_3)_2CH$=$CH_2$), 21.9 ($C(CH_3)_2CH$=$CH_2$), 18.9 ($N^+CH_2CH$=$C(CH_3)_2$).

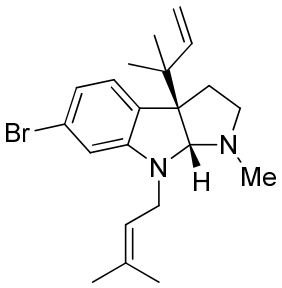
**IR** (ATR): $\tilde{\nu}$ = 3366 $cm^{-1}$ (w, br), 2969 (m), 2927 (m), 2727 (w), 1693 (s), 1602 (s), 1414 (s), 1370 (m), 1318 (w), 1150 (w), 1109 (w), 1066 (w), 1012 (w), 921 (w), 839 (m), 814 (m), 775 (w), 734 (w), 664 (w), 607 (m), 583 (m).

**UV** (MeOH): $\lambda_{max}$ (log ε) = 460 nm (1.67), 286 (3.61), 223 (4.27), 202 (4.34).

**MS** (ESI): *m/z* (%) = 390 (22), 389 (98), 388 (22), 387 (100), 321 (6), 320 (35), 319 (6), 318 (38), 251(8), 249 (9).

**HRMS** (ESI): calcd. for $C_{21}H_{28}BrN_2^+$ $[M]^+$ 387.1430,
found 387.1433.

**6-Bromo-1-methyl-8-(3-methylbut-2-en-1-yl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, *rac*-flustramine A (9)**




**9**

Indole derivative **25** (13 mg, 0.027 mmol, 1.0 eq.) in MeOH (6 mL) was added to $NaBH_4$ (0.86 mg, 0.22 mmol, 0.8 eq.) under Ar, at rt. The reaction mixture was stirred further for 24 h at rt and diluted cautiously with $H_2O$ (10 mL), followed by 2 N NaOH (20 mL). The aqueous phase was extracted with TBME (3 x 30 mL). The combined organic layers were washed with $H_2O$ (3 x 30 mL), brine (30 mL), dried over $Na_2SO_4$; filtered, and concentrated in vacuum. The residual crude was purified by chromatography (silica gel, EtOAc/petrolether (1:8 to 1:2) to obtain the title compound **9** (5.8 mg, 0.015 mmol, 54%) as a colorless oil.

**TLC** [silica gel, EtOAc/petrolether (1:4)]: $R_f$ = 0.20.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 6.90 (d, $^3J$ = 7.9 Hz, 1H, 4-H), 6.70 (dd, $^4J$ = 1.8 Hz, $^3J$ = 7.9 Hz, 1H, 5-H), 6.48 (d, $^4J$ = 1.8 Hz, 1H, 7-H), 5.94 (dd, $^3J$ = 17.4, 10.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.22 (tq, $^4J$ = 1.3 Hz, $^3J$ = 8.7, 5.8 Hz, 1H, $NCH_2CH$=$C(CH_3)_2$), 5.07 (dd, $^3J$ = 10.8 Hz, $^2J$ = 1.3 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 4.99 (dd, $^3J$ = 17.4 Hz, $^2J$ = 1.4 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.36 (s, 1H, $NCHN(CH_3)CH_2CH_2$), 3.84 (d, $^3J$ = 5.9 Hz, 2H, $NCH_2CH$=$C(CH_3)_2$), 2.67 (ddd, $^3J$ = 6.7, 2.3 Hz, $^2J$ = 9.0 Hz, 1H, $CHN(CH_3)CH_2CH_2C$), 2.47-2.38 (m, 1H, $CHN(CH_3)CH_2CH_2C$), 2.43 (s, 3H, $CHN(CH_3)CH_2CH_2C$), 2.24 (ddd, $^3J$ = 6.7 Hz, $^2J$ = 11.9, 9.9 Hz, 1H,

CHN($CH_3$)$CH_2C\mathit{H}_2$C), 1.76-1.72 (m, 1H, CHN($CH_3$)$CH_2C\mathit{H}_2$C), 1.73 (s, 6H, $NCH_2CH$=C($C\mathit{H}_3$)$_2$), 1.01 (s, 3H, CHCC($C\mathit{H}_3$)$_2$CH=$CH_2$), 0.95 (s, 3H, CHCC($C\mathit{H}_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 153.5 (C-7a), 144.9 (C($CH_3$)$_2$*C*H=$CH_2$), 134.7 ($NCH_2CH$=*C*($CH_3$)$_2$), 132.5 (C-3b), 125.8 (C-4), 121.8 (C-6), 120.9 ($NCH_2$*C*H=C($CH_3$)$_2$), 119.2 (C-5), 113.1 (C($CH_3$)$_2$CH=*C*$H_2$), 109.4 (C-7), 89.4 (C-8a), 63.4 (C-3a), 53.2 (C-2), 45.9 (N*C*$H_2$CH=C($CH_3$)$_2$), 41.4 (CHC*C*($CH_3$)$_2$CH=$CH_2$), 37.8 (CHN(*C*$H_3$)$CH_2CH_2$C), 34.5 (C-3), 25.6 ($NCH_2CH$=C(*C*$H_3$)$_2$), 23.5 (C(*C*$H_3$)$_2$CH=$CH_2$), 22.5 (C(*C*$H_3$)$_2$CH=$CH_2$), 18.1 ($NCH_2CH$=C(*C*$H_3$)$_2$).

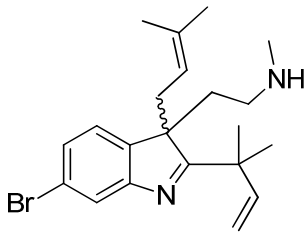
**IR** (ATR): $\tilde{\nu}$ = 3081 $cm^{-1}$ (w), 2964 (m), 2925 (m), 2853 (m), 2793 (w), 1674 (w), 1592 (s), 1487 (s), 1445 (m), 1374 (m), 1347 (w), 1314 (m), 1253 (m), 1158 (m), 1115 (w), 1091 (w), 1064 (w), 1044 (m), 1003 (m), 911 (s), 823 (m), 798 (m), 780 (m), 692 (w), 639 (w), 607 (w), 578 (w).

**UV** (MeOH): $\lambda_{max}$ (log ε) = 317 nm (3.56), 262 (3.95), 214 (4.39).

**MS** (ESI): *m/z* (%) = 392 (21), 391 (97), 390 (21), 389 (100), 360 (12), 358 (13), 323 (11), 321 (11), 309 (13), 292 (23), 290 (23), 245 (11), 180(13), 167 (14).

**HRMS** (ESI): calcd. for $C_{21}H_{30}{}^{79}BrN_2^+$ $[M+H]^+$ 389.1592,
found 389.1592.

**2-(6-Bromo-3-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)-*N*-methylethanamine (178)**




**178**

To a solution of 3-prenyl-flustrabromine (**176**, 140 mg, 0.34 mmol, 1.0 eq.) in EtOH (40 mL) was added 32% aq. NaOH (4 mL) at rt. The reaction mixture was refluxed for 3 d and cooled to rt. $H_2O$ (100 mL) was added and the reaction mixture was extracted with $Et_2O$ (4 x 100 mL), washed with $H_2O$ (3 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and filtered and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0.1)) to afford the title compound **178** (110 mg, 0.28 mmol, 83%) as a slight yellow oil.

**TLC** [silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0.1)]: $R_f$ = 0.63.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.70 (d, $^4J$ = 1.7 Hz, 1H, indole 7-H), 7.30 (dd, $^4J$ = 1.8 Hz, $^3J$ = 7.9 Hz, 1H, indole 5-H), 7.01 (d, $^3J$ = 7.9 Hz, 1 H, indole 4-H), 6.20 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, N=CC$(CH_3)_2$C*H*=$CH_2$), 5.24 (dd, $^3J$ = 17.4 Hz, $^2J$ = 0.7 Hz, 1H, C$(CH_3)_2$C*H*=C$H_2$-$H_E$), 5.16 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.8 Hz, 1H, C$(CH_3)_2$C*H*=C$H_2$-$H_Z$), 4.43-4.39 (m, 1H, N=CCC$H_2$C*H*=C$(CH_3)_2$), 2.62 (dd, $^3J$ = 6.6 Hz, $^2J$ = 15.0 Hz, 2H, N=CCC$H_2$CH=C$(CH_3)_2$), 2.31 (ddd, $^3J$ = 10.0, 4.0 Hz, $^2J$ = 14.4 Hz, 1H, CC$H_2$$CH_2$NH$CH_3$), 2.24 (s, 3H, C$CH_2$$CH_2$NHC$H_3$), 2.13 (dd, $^3J$ = 4.7 Hz, $^2J$ = 11.5 Hz, 1H, CC$H_2$$CH_2$NH$CH_3$), 2.09-2.01 (m, 1H, C$CH_2$C$H_2$NH$CH_3$), 1.84-1.77 (m, 1H, C$CH_2$C$H_2$NH$CH_3$), 1.52 (d, $^4J$ = 0.8 Hz, 3H, N=CCC$H_2$CH=C(C$H_3$)$_2$), 1.51 (s, 3H, N=CC(C$H_3$)$_2$CH=$CH_2$), 1.48 (s, 6H, N=CCC$H_2$CH=C(C$H_3$)$_2$, =CC(C$H_3$)$_2$CH=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 193.2 (indole C-2), 155.2 (indole C-7a), 144.4 (C$(CH_3)_2$*C*H=$CH_2$), 141.7 (indole C-3a), 134.5 (N=CCC$H_2$CH=*C*$(CH_3)_2$), 128.1 (indole C-5), 123.5 (indole C-7), 122.5 (indole C-4), 120.8 (indole C-6), 118.1 (C$CH_2$*C*H=C$(CH_3)_2$), 112.8 (C$(CH_3)_2$CH=*C*$H_2$), 63.2 (indole C-3), 47.0 (C$CH_2$*C*$H_2$NH$CH_3$), 43.8 (N=C*C*$(CH_3)_2$CH=$CH_2$), 36.2 (C$CH_2$$CH_2$NH*C*$H_3$)), 35.9 (C*C*$H_2$$CH_2$NH$CH_3$), 35.3 (N=CC*C*$H_2$CH=C$(CH_3)_2$), 27.7 (N=CC(*C*$H_3$)$_2$CH=$CH_2$), 27.0 (N=CC(*C*$H_3$)$_2$CH=$CH_2$), 25.6 (N=CCC$H_2$CH=C(*C*$H_3$)$_2$), 18.2 (N=CCC$H_2$CH=C(*C*$H_3$)$_2$).

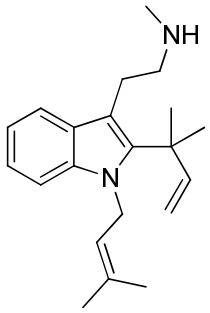
**IR** (ATR): $\tilde{\nu}$ = 3411 cm$^{-1}$ (w), 3309 (w), 3080 (w), 2964 (s), 2928 (s), 2876 (m), 2789 (w), 1710 (w), 1598 (s), 1538 (m), 1477 (s), 1451 (s), 1413 (m), 1376 (m), 1320 (w), 1242 (w), 1218 (w), 1165 (w), 1119 (m), 1036 (s), 1012 (m), 913 (s), 897 (s), 873 (w), 838 (w), 812 (m), 797 (m), 726 (w), 689 (w), 661 (w), 597 (m), 539 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 239 nm (4.00).

**MS** (EI, 70 eV): *m/z* (%) = 391 (2), 390 (8), 389 (3), 388 (8), 322 (10), 321 (68), 320 (18), 319 (100), 317 (23), 279 (15), 278 (52), 277 (18), 276 (55), 252 (39), 250 (43), 69 (40), 44 (87).

| | | |
|---|---|---|
| **HRMS** (EI): | calcd. for $C_{21}H_{29}BrN_2$ $[M]^+$ | 388.1509, |
| | found | 388.1497. |

### *N*-Methyl-2-(1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanamine (26)



**26**

To a solution of $N_a$-prenyl-debromoflustrabromine (**27**, 790 mg, 2.35 mmol, 1.0 eq.) in EtOH (30 mL) was added 32% aq. NaOH (9 mL) at rt. The reaction mixture was refluxed for 60 h and cooled to rt. $H_2O$ (50 mL) was added and the reaction mixture was extracted with EtOAc (4 x 150 mL). The combined organic layers were washed with $H_2O$ (3 x 150 mL), brine (150 mL), dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure affording the title compound **26** (728 mg, 2.19 mmol, 93 %) as a dark red oil with the smell of mint.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.59 (d, $^3J$ = 7.8 Hz, 1H, indole 4-H), 7.17-7.12 (m, 2H, indole 6-H, indole 7-H), 7.08 (ddd, $^4J$ = 2.4 Hz, $^3J$ = 5.7, 7.9 Hz, 1H, indole 5-H), 6.18 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.15-5.11 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 5.06 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 4.95 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.9 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.77 (d, $^3J$ = 5.5 Hz, 2H, $NCH_2CH$=$C(CH_3)_2$), 3.19 (t, $^3J$ = 7.8 Hz, 2H, $CCH_2CH_2NHCH_3$), 2.84 (t, $^3J$ = 7.7 Hz, 2H, $CCH_2CH_2NHCH_3$), 2.48 (s, 3H, $CCH_2CH_2NHCH_3$), 1.87 (s, br, 1H, $CCH_2CH_2NHCH_3$), 1.77 (s, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.69 (d, $^4J$ = 1.3 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.62 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 148.1 ($C(CH_3)_2CH$=$CH_2$), 140.0 (indole C-2), 136.9 (indole C-7a), 132.9 ($NCH_2CH$=$C(CH_3)_2$), 129.0 (indole C-3a), 122.2 ($NCH_2CH$=$C(CH_3)_2$), 121.3 (indole C-7), 118.8 (indole C-5), 118.2 (indole C-4), 111.6 ($C(CH_3)_2CH$=$CH_2$), 109.6 (indole C-6), 109.5 (indole C-3), 54.2 ($CCH_2CH_2NHCH_3$), 44.1 ($NCH_2CH$=$C(CH_3)_2$), 40.8 ($NCC(CH_3)_2CH$=$CH_2$), 36.4 ($CCH_2CH_2NHCH_3$)), 29.9 (2C, $NCC(CH_3)_2CH$=$CH_2$), 25.9 ($CCH_2CH_2NHCH_3$), 25.4 ($NCH_2CH$=$C(CH_3)_2$), 18.3 ($NCH_2CH$=$C(CH_3)_2$).

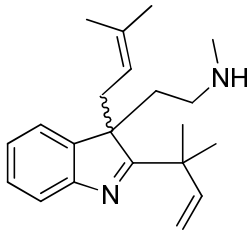
**IR** (ATR): $\tilde{\nu}$ = 3049 cm$^{-1}$ (w), 2969 (w), 2928 (w), 2873 (w), 2790 (w), 1632 (w), 1469 (m), 1447 (m), 1378 (w), 1350 (w), 1327 (w), 1309 (m), 1258 (w), 1178 (w), 1113 (w), 1018 (w), 997 (w), 912 (m), 837 (w), 738 (s), 709 (m), 597 (w), 532 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 290 nm (3.83), 240 (4.11), 231 (3.70).

**MS** (EI, 70 eV): *m/z* (%) = 310 (3), 268 (18), 267 (84), 266 (23), 252 (5), 200 (5), 199 (43), 198 (100), 196 (11), 185 (5), 184 (34), 183 (33), 182 (26), 181 (8), 180 (9), 169 (6), 168 (16), 167 (19), 154 (5), 130 (5), 69 (37).

**GC-HRMS** (EI): calcd. for $C_{21}H_{30}N_2$ $[M]^+$ 310.2409,
found 310.2421.

### *N*-Methyl-2-(3-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)ethanamine (177)




**177**

To a solution of 3-prenyl-debromo-flustrabromine (**174**, 590 mg, 1.74 mmol, 1.0 eq.) in EtOH (30 mL) was added 32% aq. NaOH (7 mL) at rt. The reaction mixture was refluxed for 60 h and cooled to rt. $H_2O$ (50 mL) was added and the reaction mixture was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL), brine (100 mL), dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure affording the title compound **177** (463 mg, 1.49 mmol, 86 %) as a dark red oil with smell of mint.

**TLC** [silica gel, $CHCl_3$/MeOH/$NH_4OH$ (9:1:0.1)]: $R_f$ = 0.38.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.49 (d, $^3J$ = 7.7 Hz, 1H, indole 7-H), 7.24-7.20 (m, 1H, indole 6-H), 7.12-7.06 (m, 2H, indole 4-H, indole 5-H), 6.16 (dd, $^3J$ = 17.5, 10.6 Hz, 1H, N=CC$(CH_3)_2$C*H*=$CH_2$), 5.16 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.9 Hz, 1H, C$(CH_3)_2$CH=C*H*$_2$-$H_E$), 5.08 (dd, $^3J$ = 10.6 Hz, $^2J$ = 1.0 Hz, 1H, C$(CH_3)_2$CH=C*H*$_2$-$H_Z$), 4.35-4.31 (m, 1H, N=CCC$H_2$C*H*=C$(CH_3)_2$), 2.61 (dd, $^3J$ = 6.2 Hz, $^2J$ = 15.0 Hz, 1H, N=CCC*H*$_2$CH=C$(CH_3)_2$), 2.52 (dd, $^3J$ = 7.1 Hz, $^2J$ = 15.0 Hz, 1H, N=CCC*H*$_2$CH=C$(CH_3)_2$), 2.27-2.19 (m, 1H, CC*H*$_2$$CH_2$NH$CH_3$), 2.14 (s, 3H, $CCH_2CH_2$NHC*H*$_3$), 2.08-2.01 (m, 1H, CC*H*$_2$$CH_2$NH$CH_3$), 1.96 (dt, $^3J$ = 4.0 Hz, $^2J$ = 11.0 Hz, 1H, $CCH_2$C*H*$_2$NH$CH_3$), 1.74-1.67 (m, 1H, $CCH_2$C*H*$_2$NH$CH_3$), 1.46 (s, 3H, N=CC(C*H*$_3$)$_2$CH=$CH_2$), 1.43 (d, $^4J$ = 1.1 Hz, 3H, N=CC(C*H*$_3$)$_2$CH=$CH_2$), 1.42 (s, 3H, N=CCC$H_2$CH=C(C*H*$_3$)$_2$), 1.42 (s, 3H, N=CCC$H_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 191.3 (indole C-2), 153.8 (indole C-7a), 144.8 ($C(CH_3)_2CH=CH_2$), 142.7 (indole C-3a), 133.9 ($N=CCCH_2CH=C(CH_3)_2$), 127.5 (indole C-6), 125.3 (indole C-5), 121.3 (indole C-4), 120.0 (indole C-7), 118.5 ($CCH_2CH=C(CH_3)_2$), 112.3 ($C(CH_3)_2CH=CH_2$), 63.2 (indole C-3), 47.2 ($CCH_2CH_2NHCH_3$), 43.6 ($N=CC(CH_3)_2CH=CH_2$), 36.3 ($CCH_2CH_2NHCH_3$)), 36.3 ($CCH_2CH_2NHCH_3$), 35.4 ($N=CCCH_2CH=C(CH_3)_2$), 27.7 ($N=CC(CH_3)_2CH=CH_2$), 27.0 ($N=CCCH_2CH=C(CH_3)_2$), 25.5 ($N=CC(CH_3)_2CH=CH_2$), 18.2 ($N=CCCH_2CH=C(CH_3)_2$).

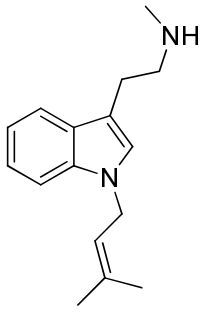
**IR** (ATR): $\tilde{\nu}$ = 3305 cm$^{-1}$ (w), 3079 (w), 2966 (m), 2927 (m), 2875 (m), 2790 (w), 1634 (w), 1607 (w), 1541 (m), 1455 (s), 1413 (w), 1376 (m), 1320 (w), 1240 (w), 1218 (w), 1112 (m), 1034 (m), 1012 (m), 914 (m), 838 (w), 759 (s), 740 (s), 684 (w), 624 (w), 590 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 263 nm (3.82), 239 (3.74).

**MS** (EI, 70 eV): *m/z* (%) = 310 (4), 266 (13), 253 (8), 252 (15), 242 (12), 241 (62), 240 (8), 239 (28), 310 (11), 199 (24), 198 (100), 197 (5), 196 (15), 194 (5), 185 (14), 184 (37), 183 (28), 182 (32), 181 (8), 180 (12), 173 (8), 172 (22), 171 (9), 170 (10), 169 (9), 168 (22), 167 (19), 156 (5), 154 (7), 130 (8), 115 (6), 69 (22), 44 (39).

**GC-HRMS** (EI): calcd. for $C_{21}H_{30}N_2$ $[M]^+$ 310.2409,
found 310.2398. [deviation?]

### *N*-Methyl-2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)ethanamine (192a)




**192a**

To a solution of $N_a$-prenyl-$N_b$-formyl-$N_b$-methyltryptamine (**146**, 1.43 g, 5.29 mmol, 1.0 eq.) in EtOH (120 mL) was added 32% aq. NaOH (25 mL) at rt. The reaction mixture was refluxed for 48 h and cooled to rt and concentrated to volume of 40 mL. $H_2O$ (150 mL) was added and the reaction mixture was extracted with EtOAc (3 x 100 mL), washed with $H_2O$ (4 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and filtered. The solvent was removed under reduced pressure affording the title compound **192a** (1.20 g, 4.96 mmol, 94 %) as a orange oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.61 (d, $^3J$ = 7.9 Hz, 1H, indole 4-H), 7.29 (d, $^3J$ = 8.2 Hz, 1H, indole 7-H), 7.19 (ddd, $^4J$ = 1.1 Hz, $^3J$ = 8.1, 7.1 Hz, 1H, indole 6-H), 7.09 (ddd, $^4J$ = 0.9 Hz, $^3J$ = 7.8, 7.0 Hz, 1H, indole 5-H), 6.93 (s, 1H, indole 2-H), 5.40-5.32 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.64 (d, $^3J$ = 6.9 Hz, 2H, $NCH_2CH$=$C(Me)_2$), 3.01-2.85 (m, 4H, $CCH_2CH_2NHCH_3$), 2.43 (s, 3H, $CCH_2CH_2NHCH_3$), 1.81 (s, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.81 (s, 1H, $CCH_2CH_2NHCH_3$), 1.75 (d, $^4J$ = 0.9 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 136.4 (indole C-7a), 136.0 ($NCH_2CH$=$C(CH_3)_2$), 128.1 (indole C-3a), 125.3 (indole C-2), 121.4 (indole C-6), 120.1 ($NCH_2CH$=$C(CH_3)_2$), 119.0 (indole C-4), 118.7 indole C-5), 112.4 (indole C-3), 109.5 (indole C-7), 52.1 ($CCH_2CH_2NHCH_3$), 43.9 ($NCH_2CH$=$C(CH_3)_2$), 36.3 ($CCH_2CH_2NHCH_3$), 25.62 ($NCH_2CH$=$C(CH_3)_2$), 25.55 ($CCH_2CH_2NHCH_3$), 18.0 ($NCH_2CH$=$C(CH_3)_2$).

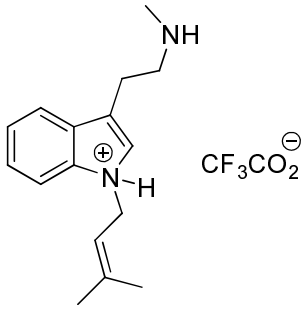
**IR** (ATR): $\tilde{\nu}$ = 3317 cm$^{-1}$ (w), 3051 (w), 2968 (w), 2913 (w), 2848 (w), 2791 (w), 1468 (m), 1443 (m), 1374 (w), 1332 (w), 1311 (w), 1172 (w), 1109 (w), 1013 (w), 846 (w), 734 (s).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 293 nm (3.73), 240 (3.98), 232 (3.68).

**MS** (EI, 70 eV): *m/z* (%) = 242 (4), 200 (12), 199 (84), 198 (10), 132 (5), 131 (54), 130 (100), 129 (12), 102 (8), 77 (5), 69 (22), 44 (30).

**HRMS** (EI): calcd. for $C_{16}H_{22}N_2$ $[M]^+$ 242.1778,
found 242.1716.

**3-(2-(Methylamino)ethyl)-1-(3-methylbut-2-enyl)-1*H*-indolium 2,2,2-trifluoroacetate (192b)**




**192b**

To a solution of $N_a$-prenyl-$N_b$-methyltryptamine (**192a**, 300 mg, 1.24 mmol, 1.0 eq.) in DCM (20 mL) was added TFA (0.46 mL, 6.19 mmol, 5.0 eq.) at rt over 5 min. The reaction mixture was stirred at rt for 1 h diluted with DCM (100 mL). The organic layer was washed with $H_2O$ (3 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and filtered. The solvent was removed under reduced pressure and the residue obtained

was purified by column chromatography (silica gel, CHCl3/MeOH (5:1)) to obtain the title compound **192b** (46 mg, 0.24 mmol, 19%) as an orange oil.

**TLC** [silica gel, $CHCl_3$/MeOH (5:1)]: $R_f$ = 0.48.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.55 (dd, $^4J$ = 0.9 Hz, $^3J$ = 7.9 Hz, 1H, indole 4-H), 7.28 (d, $^3J$ = 8.2 Hz, 1H, indole 7-H), 7.19 (ddd, $^4J$ = 1.1 Hz, $^3J$ = 8.2, 7.0 Hz, 1H, indole 6-H), 7.12 (s, br, 1H, CHCN*H*$^+$CH), 7.09 (ddd, $^4J$ = 1.0 Hz, $^3J$ = 8.0, 7.0 Hz, 1H, indole 5-H), 6.95 (s, 1H, indole 2-H), 5.30-5.35 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 4.61 (d, $^3J$ = 6.9 Hz, 2H, $NCH_2CH$=$C(Me)_2$), 3.11 (s, 4H, $CCH_2CH_2NHCH_3$), 2.56 (s, 3H, $CCH_2CH_2NHCH_3$), 1.80 (d, $^4J$ = 0.5 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.75 (d, $^4J$ = 1.1 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 136.4 (indole C-7a), 136.3 ($NCH_2CH$=$C(CH_3)_2$), 127.6 (indole C-3a), 125.7 (indole C-2), 121.7 (indole C-6), 119.8 ($NCH_2CH$=$C(CH_3)_2$), 119.1 (indole C-5), 118.6 indole C-4), 109.7 (indole C-7), 109.5 (indole C-3), 50.6 ($CCH_2CH_2NHCH_3$), 44.0 ($NCH_2CH$=$C(CH_3)_2$), 36.9 ($CCH_2CH_2NHCH_3$), 25.6 ($NCH_2CH$=$C(CH_3)_2$), 23.1 ($CCH_2CH_2NHCH_3$), 18.0 ($NCH_2CH$=$C(CH_3)_2$).

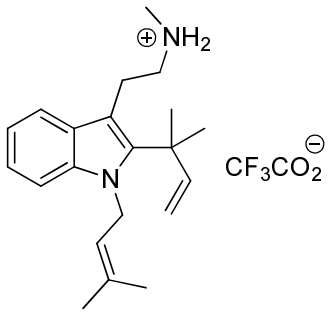
**IR** (ATR): $\tilde{\nu}$ = 3050 cm$^{-1}$ (w), 2970 (w), 2916 (w), 2858 (w), 2482 (w), 1673 (s), 1466 (m), 1378 (w), 1334 (w), 1199 (s), 1173 (s), 1128 (s), 1014 (w), 831 (m), 798 (m), 739 (s), 720 (s).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 290 nm (3.62), 240 (3.76).

**MS** (EI, 70 eV): *m/z* (%) = 242 (4), 240 (4), 200 (10), 199 (64), 198 (10), 143 (5), 132 (5), 131 (49), 130 (100), 129 (7), 102 (5), 69 (20):

| | | |
|---|---|---|
| **HRMS** (ESI): | calcd. for $C_{16}H_{23}N_2$ $[M]^+$ | 243.1856, |
| | found | 243.1857. |

**_N_-Methyl-2-(1-(3-methylbut-2-enyl)-2-(2-methylbut-3-en-2-yl)-1_H_-indol-3-yl)ethanaminium 2,2,2-trifluoroacetate (193)**



**193**

To a solution of $N_a$-prenyl-debromodeformylflustrabromine (**26**, 98 mg, 0.32 mmol, 1.0 eq.) in toluene (6 mL) was added TFA (18 mg, 0.15 mmol, 1 eq.) at rt. The reaction mixture and a magnet stir bar were sealed in the reaction vessel of an MLS START 1500 microwave synthesizer and irradiated at 150 °C for 1 h. To the cooled reaction mixture, EtOAc (200 mL) was added. The reaction mixture was washed with $H_2O$ (4 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residual oil was purified by column chromatography (silica gel, $CHCl_3$/MeOH (9:1 to 4:1)) to obtain the title compound **193** (90 mg, 0.21 mmol, 67%) as a red oil.

**TLC** [silica gel, $CHCl_3$/MeOH (9:1)]: $R_f$ = 0.38.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.66 (d, $^3J$ = 7.7 Hz, 1H, indole 4-H), 7.17-7.11 (m, 2H, indole 6-H, indole 7-H), 7.11-7.07 (m, 1H, indole 5-H), 6.17 (dd, $^3J$ = 17.5, 10.5 Hz, 1H, $C(CH_3)_2CH$=$CH_2$), 5.15 (s, br, 2H, $CCH_2CH_2NH_2^+CH_3$), 5.13-5.10 (m, 1H, $NCH_2CH$=$C(CH_3)_2$), 5.06 (dd, $^3J$ = 10.6 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_Z$), 4.94 (dd, $^3J$ = 17.5 Hz, $^2J$ = 0.8 Hz, 1H, $C(CH_3)_2CH$=$CH_2$-$H_E$), 4.77 (d, $^3J$ = 5.4 Hz, 2H, $NCH_2CH$=$C(CH_3)_2$), 3.39-3.35 (m, 2H, $CCH_2CH_2NH_2^+CH_3$), 2.97-2.93 (m, 2H, $CCH_2CH_2NH_2^+CH_3$), 2.58 (s, 3H, $CCH_2CH_2NH_2^+CH_3$), 1.77 (s, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.69 (d, $^4J$ = 1.2 Hz, 3H, $NCH_2CH$=$C(CH_3)_2$), 1.61 (s, 6H, $C(CH_3)_2CH$=$CH_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 147.8 ($C(CH_3)_2CH$=$CH_2$), 140.3 (indole C-2), 136.9 (indole C-7a), 133.1 ($NCH_2CH$=$C(CH_3)_2$), 128.7 (indole C-3a), 122.1 ($NCH_2CH$=$C(CH_3)_2$), 121.5 (indole C-7), 119.1 (indole C-5), 118.1 (indole C-4), 111.8 ($C(CH_3)_2CH$=$CH_2$), 109.6 (indole C-6), 108.1 (indole C-3), 52.8 ($CCH_2CH_2NH_2^+CH_3$), 44.1 ($NCH_2CH$=$C(CH_3)_2$), 40.8 ($NCC(CH_3)_2CH$=$CH_2$), 35.0 ($CCH_2CH_2NH_2^+CH_3$), 29.8 (2C, $NCC(CH_3)_2CH$=$CH_2$), 25.4 ($NCH_2CH$=$C(CH_3)_2$), 24.6 ($CCH_2CH_2NH_2^+CH_3$), 18.2 ($NCH_2CH$=$C(CH_3)_2$).

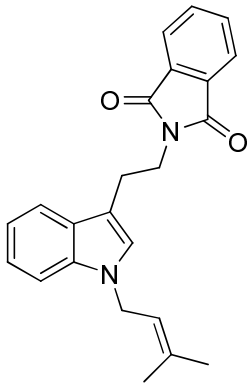
**IR** (ATR): $\tilde{\nu}$ = 2969 $cm^{-1}$ (w), 2926 (m), 2868 (w), 2784 (w), 2698 (w), 2468 (w), 2439 (w), 1632 (w), 1582 (w), 1470 (s), 1379 (w), 1351 (m), 1329 (w), 1308 (m), 1183 (w), 1115 (w), 1019 (w), 997 (w), 910 (m), 836 (w), 740 (s), 710 (m), 580 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 290 nm (3.95), 240 (4.18), 231 (3.78).

**MS** (EI, 70 eV): *m/z* (%) = 312 (23), 311 (100), 281 (12), 280 (58), 212 (12).

**HRMS** (ESI): calcd. for $C_{21}H_{31}N_2$ $[M+H]^+$ 311.2482,
found 311.2484.

**2-(2-(1-(3-Methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (208):**



**208**

To NaH (60% in mineral oil, 433 mg, 10.82 mmol, 1.5 eq.) was added pentane (2 mL) at rt and stirred for 2 min. Pentane was removed via syringe. The reaction mixture was cooled on an ice bath and phthaloyltryptamine (**165**, 2.0 g, 7.21 mmol, 1.0 eq.) in DMF (25 mL) was added within 2 min and stirred for 1 h at 0 °C. To the red colored reaction mixture, prenylbromide (1.32 mL, 10.82 mmol, 1.5 eq.) in DMF (2 mL) was added drop wise. The reaction mixture was allowed to warm to rt and stirred at rt for 24 h. $H_2O$ (50 mL) was cautiously added and the reaction mixture was extracted with TBME (4 x 100 mL). The combined etherial layers were washed with $H_2O$ (3 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc/petrolether (1:4 to 1:1)) to obtain the title compound **208** (2.32 g, 6.48 mmol, 90%) as a yellow solid.

**TLC** [silica gel, EtOAc/petrolether (1:4)]: $R_f$ = 0.48.

**Mp**: 132-134 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.86-7.81 (m, 2H, N(C(=O)CC*H*CH)$_2$), 7.73 (d, $^3J$ = 7.8 Hz, 1H, indole 4-H), 7.70-7.67 (m, 2H, N(C(=O)CCHC*H*)$_2$), 7.29 (d, $^3J$ = 8.2 Hz, 1H, indole 7-H), 7.23-7.15 (m, 1H, indole 6-H), 7.11 (ddd, $^3J$ = 7.3, 7.1 Hz, $^4J$ = 1.0 Hz, 1H, indole 5-H), 6.99 (s, 1H, indole 2-H), 5.38-5.29 (m, 1H, $NCH_2C\mathit{H}=C(CH_3)_2$), 4.63 (d, $^3J$ = 6.9 Hz, 2H, $NC\mathit{H}_2CH=C(CH_3)_2$), 4.02-3.94 (m, 2H,

$CCH_2CH_2N$(phthaloyl)), 3.16-3.08 (m, 2H, $CCH_2CH_2N$(phthaloyl), 1.80 (s, 3H, $NCH_2CH=C(CH_3)_2$), 1.75 (d, $^4J$ = 1.0 Hz, 3H, $NCH_2CH=C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.3 (2C, N(*C*(=O)CCHCH)$_2$), 136.3 (indole C-7a), 136.2 ($NCH_2CH=C(CH_3)_2$) 133.8 (2C, N(C(=O)CCH*C*H)$_2$), 132.3 (2C, N(C(=O)*C*CHCH)$_2$), 128.0 (indole C-3a), 125.4 (indole C-2), 123.1 (2C, N(C(=O)C*C*HCH)$_2$), 121.5 (indole C-6), 120.0 ($NCH_2CH=C(CH_3)_2$), 119.0 (indole C-4), 118.9 (indole C-5), 110.8 (indole C-3), 109.4 (indole C-7), 43.9 ($NCH_2CH=C(CH_3)_2$), 38.7 ($CCH_2CH_2N$(phthaloyl)), 25.6 ($NCH_2CH=C(CH_3)_2$), 24.5 ($CCH_2CH_2N$(phthaloyl)), 18.0 ($NCH_2CH=C(CH_3)_2$).

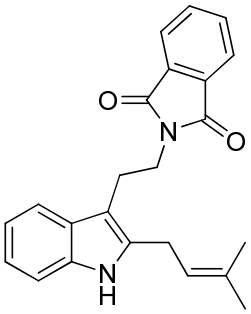
**IR** (ATR): $\tilde{\nu}$ = 3056 cm$^{-1}$ (w), 2996 (w), 2941 (w), 2912 (w), 2859 (w), 1766 (w), 1700 (s), 1611 (w), 1468 (m), 1433 (m), 1397 (s), 1356 (s), 1334 (m), 1272 (w), 1241 (w), 1220 (w), 1171 (m), 1125 (w), 1083 (s), 1011 (m), 992 (w), 949 (w), 869 (w), 840 (w), 820 (w), 800 (w), 730 (s), 715 (s), 689 (m), 642 (w), 606 (w), 574 (w).

**UV** ($CH_3CN$): $\lambda_{max}$ (log ε) = 292 nm (3.85), 241 (4.24).

**MS** (EI, 70 eV): *m/z* (%) = 359 $[M+H]^+$ (7), 358 $[M]^+$ (24), 199 (7), 198 (48), 161 (8), 160 (63), 143 (12), 133 (14), 131 (12), 130 (100), 129 (30), 128 (7), 115 (8), 105 (11), 104 (14), 103 (8), 102 (16), 69 (25).

**GC-HRMS** (EI): calcd. for $C_{23}H_{22}N_2O_2$ $[M]^+$ 358.1676,
found 358.1691.

**2-(2-(2-(3-Methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (29):**



**29**

To a solution of *N*$^b$-phthaloyltryptamine (**165**, 7.0 g, 25.24 mmol, 1.0 eq.) and $Et_3N$ (4.55 mL, 32.82 mmol, 1.3 eq.) in DCM (200 mL) was added *tert*-BuOCl (**137**, 3.71 mL, 32.82 mmol, 1.3 eq.) at –78 °C over 10 min and stirred at –78 °C for 45 min. Tri(*n*-butyl)prenylstannane[137] (**203**, 32.42 mL, 96.48 mmol, 3.82 eq.) was added, followed by rapid addition of $BCl_3$ (1.0 M in DCM, 60.60 mL, 60.60 mmol, 2.4 eq.) within 3 min. The reaction

137. Y. Naruta, Y- Nishigaichi, K. Maruyama, *Chem. Lett.***1986**, *11*,1857–1860.

mixture was stirred at –78 °C for 1 h, poured into sat. $NaHCO_3$ (200 mL) to quench and stirred at rt for 10 min. Both layers were filtered through celite-545 and separated. The aqueous layer is extracted with DCM (3 x 100 mL). To the combined organic layers, sat. KF (200 mL) was added and stirred at rt for 30 min and both layers were filtered through celite-545. The separated organic phase was washed with sat. KF (1 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel + KF (10%, w/w), EtOAc/petrolether (1:4 to 1:1)) to afford the title compound **29** (2.4 g, 6.70 mmol, 27%) as a slightly orange solid.

**TLC** [silica gel, EtOAc/petrolether (1:4)]: $R_f$ = 0.32.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.85 (s, br, 1H, CHCN*H*CCH$_2$), 7.83-7.81 (m, 2H, N(C(=O)CC*H*CH)$_2$), 7.70-7.66 (m, 3H, N(C(=O)CCHC*H*)$_2$, indole 4-H), 7.26-7.24 (m, 1H, indole 7-H), 7.11-7.04 (m, 2H, indole 5-H, indole 6-H), 5.31-5.25 (m, 1H, NHCCH$_2$C*H*=C(CH$_3$)$_2$), 3.91-3.87 (m, 2H, CCH$_2$C*H*$_2$N(phthaloyl)), 3.49 (d, $^3J$ = 7.3 Hz, 2H, NHCC*H*$_2$CH=C(CH$_3$)$_2$), 3.09-3.05 (m, 2H, CC*H*$_2$CH$_2$N(phthaloyl), 1.75 (s, 6H, NHCCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.3 (2C, N(*C*(=O)CCHCH)$_2$), 135.1 (2C, indole C-2, indole C-7a), 134.7 (NHCCH$_2$CH=*C*(CH$_3$)$_2$) 133.8 (2C, N(C(=O)CCH*C*H)$_2$), 132.2 (2C, N(C(=O)*C*CHCH)$_2$), 128.6 (indole C-3a), 123.1 (2C, N(C(=O)C*C*HCH)$_2$), 121.1 (indole C-6), 120.2 (NHCCH$_2$*C*H=C(CH$_3$)$_2$), 119.4 (indole C-5), 118.1 (indole C-4), 110.3 (indole C-7), 107.2 (indole C-3), 38.4 (NHC*C*H$_2$CH=C(CH$_3$)$_2$), 25.0 (CCH$_2$*C*H$_2$N(phthaloyl)), 25.7 (NHCCH$_2$CH=C(*C*H$_3$)$_2$), 23.4 (C*C*H$_2$CH$_2$N(phthaloyl)), 17.8 (NHCCH$_2$CH=C(*C*H$_3$)$_2$).

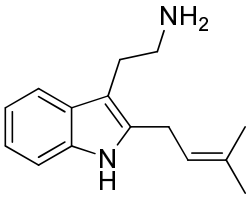
**IR** (ATR): $\tilde{\nu}$ = 3385 cm$^{-1}$ (w), 3057 (w), 2972 (w), 2932 (w), 2863 (w), 1769 (w), 1701 (s), 1613 (w), 1463 (m), 1441 (m), 1395 (s), 1359 (m), 1187 (w), 1120 (w), 1099 (w), 1021 (m), 965 (w), 865 (w), 743 (m), 715 (s).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 352 nm (2.80), 284 (3.85), 241 (4.19), 234 (3.83).

**MS** (EI, 70 eV): *m/z* (%) = 359 [M+H]$^+$ (8), 358 [M]$^+$ (27), 199 (17), 198 (100), 195 (8), 184 (8), 183 (10), 182 (12), 169 (7), 168 (13), 167 (7), 160 (6), 156 (10), 155 (6), 143 (10), 130 (10), 77 (5).

**GC-HRMS** (EI): calcd. for $C_{23}H_{22}N_2O_2$ [M]$^+$ 358.1676,
found 358.1654.

**2-(2-(3-Methylbut-2-enyl)-1*H*-indol-3-yl)ethanamine (213):**




**213**

To a solution of 2-prenyl-phthaloyltryptamine (**29**, 1.20 g, 3.35 mmol, 1.0 eq.) in EtOH (110 mL) was added hydrazine monohydrate (1.9 mL, 40.17 mmol, 12.0 eq.) at rt. The reaction mixture was refluxed for 24 h . After cooling to rt, the reaction mixture was diluted with isopropanol/$CHCl_3$ (2:1, 400 mL) and washed with $H_2O$ (1 x 200 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The crude reaction mixture was purified by column chromatography (silica gel, $CHCl_3$/MeOH/$NH_4OH$ (7:1:0 to 4:1:0.1)) to afford the title compound **213** (623 mg, 2.73 mmol, 82%) as a yellow oil.

**TLC** [silica gel, $CHCl_3$/MeOH/$NH_4OH$ (4:1:0.1)]: $R_f$ = 0.64.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.99 (s, br, 1H, CHCN*H*CCH$_2$), 7.55 (d, $^3J$ = 7.3 Hz, 1H, indole 4-H), 7.23 (dd, $^4J$ = 0.9 Hz, $^3J$ = 6.8 Hz, 1H, indole 7-H), 7.07 (dt, $^4J$ = 1.4 Hz, $^3J$ = 7.5 Hz, 1H, indole 6-H), 7.03 (dt, $^4J$ = 1.3 Hz, $^3J$ = 7.4 Hz, 1H, indole 5-H), 5.29-5.25 (m, 1H, NHCCH$_2$C*H*=C(CH$_3$)$_2$), 4.29 (s, br, 2H, CCH$_2$CH$_2$N*H*$_2$), 3.45 (d, $^3J$ = 7.2 Hz, 2H, NHCC*H*$_2$CH=C(CH$_3$)$_2$), 3.01-2.93 (m, 4H, CC*H*$_2$C*H*$_2$NH$_2$), 3.49 (d, $^3J$ = 7.3 Hz, 2H, 1.74 (s, 3H, NHCCH$_2$CH=C(C*H*$_3$)$_2$), 1.72 (s, 3H, NHCCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 135.4 (indole C-2), 135.2 (indole C-7a), 134.6 (NHCCH$_2$CH=*C*(CH$_3$)$_2$) 128.6 (indole C-3a), 121.0 (indole C-6), 120.2 (NHCCH$_2$*C*H=C(CH$_3$)$_2$), 119.2 (indole C-5), 118.0 (indole C-4), 110.4 (indole C-7), 107.0 (indole C-3), 41.6 (CCH$_2$*C*H$_2$NH$_2$), 25.9 (NHC*C*H$_2$CH=C(CH$_3$)$_2$), 25.7 (NHCCH$_2$CH=C(*C*H$_3$)$_2$), 25.0 (C*C*H$_2$CH$_2$NH$_2$), 17.9 (NHCCH$_2$CH=C(*C*H$_3$)$_2$).

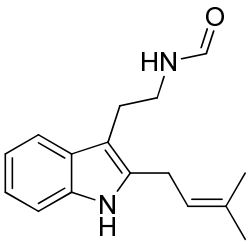
**IR** (ATR): $\tilde{\nu}$ = 3397 cm$^{-1}$ (w), 3294 (w), 3054 (w), 2967 (m), 2916 (m), 2856 (m), 1585 (m), 1460 (m), 1375 (w), 1341 (w), 1306 (w), 1241 (w), 1099 (m), 1011 (w), 920 (w), 741 (s), 619 (w).

**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 282 nm (3.65), 240 (3.76).

**MS** (EI, 70 eV): *m/z* (%) = 229 $[M+H]^+$ (4), 228 $[M]^+$ (24), 212 (5), 211 (31), 199 (33), 198 (100), 197 (8), 196 (23), 194 (5), 184 (14), 183 (24), 182 (30), 181 (13), 180 (12), 170 (7), 169 (19), 168 (30), 167 (23), 157 (6), 156 (22), 155 (13), 154 (11), 144 (13), 143 (22), 142 (6), 131 (6), 130 (24), 129 (8), 128 (7), 115 (9), 77(8).

**GC-HRMS** (EI): calcd. for $C_{15}H_{20}N_2$ $[M]^+$ 228.1621,
found 228.1625.

***N*-(2-(2-(3-Methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)formamide (30):**



**30**

A mixture of $Ac_2O$ (0.21 mL, 2.17 mmol, 5.0 eq.) and $HCO_2H$ (0.08 mL, 2.17 mmol, 5.0 eq.) was stirred at 60 °C for 1 h. After cooling to rt, a solution of 2-prenyltryptamine (**213**, 99 mg, 0.43 mmol, 1.0 eq.) in DCM (10 mL) was added drop wise. The reaction mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was added to aqueous NaOH (12 M, 10 mL) and ice (15 g). The alkaline mixture was diluted with DCM (50 mL) and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were washed with HCl (2 M, 2 x 30 mL), $H_2O$ (3 x 50 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum to afford compound **30** (108 mg, 0.42 mmol, 97%) as an oil.

Ratio of rotamers in $CDCl_3$: 1:0.2.

**TLC** [silica gel, $CHCl_3$/MeOH (8:1)]: $R_f$ = 0.66.

Major Rotamer:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 8.06 (d, $^4J$ = 1.3 Hz, 1H, C*C*$H_2$CH$_2$NHC*H*O), 7.99 (s, br, 1H, CHCN*H*CCH$_2$), 7.50 (d, $^3J$ = 7.7 Hz, 1H, indole 4-H), 7.30-7.27 (m, 1H, indole 7-H), 7.15-7.11 (m, 1H, indole 6-H), 7.10-7.06 (m, 1H, indole 5-H), 5.60 (s, br, 1H, C*C*H$_2$CH$_2$N*H*CHO), 5.31-5.26 (m, 1H, NHCCH$_2$C*H*=C(CH$_3$)$_2$), 3.56 (q, $^3J$ = 6.4 Hz, 2H, CCH$_2$C*H*$_2$NHCHO), 3.45 (d, $^3J$ = 6.7 Hz, 2H, NHCC*H*$_2$CH=C(CH$_3$)$_2$), 2.95 (t, $^3J$ = 6.7 Hz, 2H, CC*H*$_2$CH$_2$NHCHO), 1.77 (s, 3H, NHCCH$_2$CH=C(C*H*$_3$)$_2$), 1.76 (s, 3H, NHCCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 161.1 ($CH_2NHCHO$), 135.4 (indole C-2), 135.2 (indole C-7a), 134.8 ($NHCCH_2CH=C(CH_3)_2$) 128.6 (indole C-3a), 121.3 (indole C-6), 120.2 ($NHCCH_2CH=C(CH_3)_2$), 119.5 (indole C-5), 117.9 (indole C-4), 110.7 (indole C-7), 107.4 (indole C-3), 38.5 ($CCH_2CH_2NHCHO$), 25.7 ($NHCCH_2CH=C(CH_3)_2$), 25.1 ($NHCCH_2CH=C(CH_3)_2$), 23.9 ($CCH_2CH_2NHCHO$), 17.9 ($NHCCH_2CH=C(CH_3)_2$).

Minor Rotamer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.84 (s, 1H, $CHCNHCCH_2$), 7.81 (s, 1H, $CCH_2CH_2NHCHO$), 7.46 (d, $^3J$ = 7.7 Hz, 1H, indole 4-H), 7.30-7.27 (m, 1H, indole 7-H), 7.15-7.11 (m, 1H, indole 6-H), 7.10-7.06 (m, 1H, indole 5-H), 5.60 (s, br, 1H, $CCH_2CH_2NHCHO$), 5.31-5.26 (m, 1H, $NHCCH_2CH=C(CH_3)_2$), 3.45 (d, $^3J$ = 6.7 Hz, 2H, $NHCCH_2CH=C(CH_3)_2$), 3.43-3.39 (m, 2H, $CCH_2CH_2NHCHO$), 2.90 (t, $^3J$ = 6.6 Hz, 2H, $CCH_2CH_2NHCHO$), 1.77 (s, 3H, $NHCCH_2CH=C(CH_3)_2$), 1.76 (s, 3H, $NHCCH_2CH=C(CH_3)_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($CH_2NHCHO$), 135.5 (indole C-2), 135.0 (indole C-7a), 134.8 ($NHCCH_2CH=C(CH_3)_2$) 128.6 (indole C-3a), 121.4 (indole C-6), 120.0 ($NHCCH_2CH=C(CH_3)_2$), 119.5 (indole C-5), 117.6 (indole C-4), 110.5 (indole C-7), 107.4 (indole C-3), 42.1 ($CCH_2CH_2NHCHO$), 26.3 ($CCH_2CH_2NHCHO$), 25.7 ($NHCCH_2CH=C(CH_3)_2$), 25.1 ($NHCCH_2CH=C(CH_3)_2$), 17.9 ($NHCCH_2CH=C(CH_3)_2$).

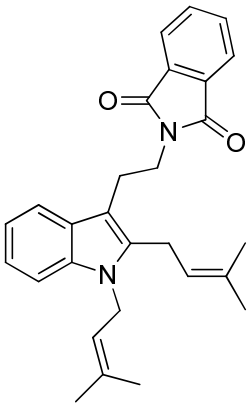
**IR** (ATR): $\tilde{\nu}$ = 3284 cm$^{-1}$ (w, br), 3057 (w), 2971 (w), 2928 (w), 2860 (w), 1657 (s, br), 1519 (w), 1455 (m), 1381 (m), 1307 (w), 1239 (w), 743 (s).

**UV** ($CH_2Cl_2$): $\lambda_{max}$ (log ε) = 283 nm (3.68), 271 (3.67), 230 (4.19).

**MS** (EI, 70 eV): *m/z* (%) = 257 $[M+H]^+$ (5), 256 $[M]^+$ (28), 211 (17), 199 (17), 198 (100), 196 (18), 184 (11), 183 (17), 182 (19), 181 (9), 180 (8), 169 (14), 168 (28), 167 (16), 156 (18), 155 (9), 154 (8), 144 (7), 143 (18), 130 (17), 115 (7), 77(5).

**GC-HRMS** (EI): calcd. for $C_{16}H_{20}N_2O$ $[M]^+$ 256.1576,
found 256.1597.

**2-(2-(1,2-Bis(3-methylbut-2-enyl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (214):**



**214**

To NaH (60% in mineral oil, 84 mg, 2.09 mmol, 1.5 eq.) was added pentane (1 mL) at rt and it was stirred for 2 min. Pentane was removed via syringe. The reaction mixture was cooled on an ice bath and 2-prenyl-phthaloyltryptamine (**29**, 500 mg, 1.39 mmol, 1.0 eq.) in DMF (25 mL) was added drop wise and stirred for 1 h at 0 °C. To the reaction mixture, prenylbromide (0.25 mL, 2.09 mmol, 1.5 eq.) in DMF (2 mL) was added drop wise. The reaction mixture was allowed to warm to rt and stirred at rt for 48 h. $H_2O$ (20 mL) was cautiously added and the reaction mixture was extracted with $Et_2O$ (3 x 100 mL). The combined etherial layers were washed with $H_2O$ (3 x 100 mL), brine (100 mL), dried over $Na_2SO_4$, and concentrated in vacuum. The residue obtained was purified by column chromatography (silica gel, EtOAc/petrolether (1:5 to 1:1)) to obtain the title compound **214** (188 mg, 0.44 mmol, 32%) as a yellow solid.

**TLC** [silica gel, EtOAc/petrolether (1:4)]: $R_f$ = 0.52.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ = 7.84 (dd, $^3J$ = 5.5, 3.0 Hz, 2H, N(C(=O)CC*H*CH)$_2$), 7.72-7.69 (m, 3H, N(C(=O)CCHC*H*)$_2$, indole 4-H), 7.21 (dd, $^4J$ = 1.0 Hz, $^3J$ = 7.2 Hz, 1H, indole 7-H), 7.15-7.06 (m, 2H, indole 5-H, indole 6-H), 5.13-5.07 (m, 2H, NCH$_2$C*H*=C(CH$_3$)$_2$, CCH$_2$C*H*=C(CH$_3$)$_2$), 4.64 (d, $^3J$ = 6.1 Hz, 2H, NC*H*$_2$CH=C(CH$_3$)$_2$), 3.89-3.85 (m, 2H, CCH$_2$C*H*$_2$N(phthaloyl)), 3.51 (d, $^3J$ = 6.5 Hz, 2H, CC*H*$_2$CH=C(CH$_3$)$_2$), 3.10-3.06 (m, 2H, CC*H*$_2$CH$_2$N(phthaloyl), 1.81 (d, $^4J$ = 0.8 Hz, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.79 (d, $^4J$ = 0.8 Hz, 3H, CCH$_2$CH=C(C*H*$_3$)$_2$), 1.68 (d, $^4J$ = 1.2 Hz, 3H, NCH$_2$CH=C(C*H*$_3$)$_2$), 1.67 (d, $^4J$ = 1.3 Hz, 3H, CCH$_2$CH=C(C*H*$_3$)$_2$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ = 168.3 (2C, N(*C*(=O)CCHCH)$_2$), 136.8 (indole C-2), 136.0 (indole C-7a), 132.7 (NCH$_2$CH=*C*(CH$_3$)$_2$), 132.3 (CCH$_2$CH=*C*(CH$_3$)$_2$), 133.8 (2C, N(C(=O)CCH*C*H)$_2$), 133.7 (2C, N(C(=O)*C*CHCH)$_2$), 127.9 (indole C-3a), 123.1 (2C, N(C(=O)C*C*HCH)$_2$), 120.8 (indole C-6), 121.5 (NCH$_2$*C*H=C(CH$_3$)$_2$), 121.3 (CCH$_2$*C*H=C(CH$_3$)$_2$), 119.0 (indole C-5), 118.2 (indole C-4), 109.1 (indole C-7), 107.2 (indole C-3), 41.6 (N*C*H$_2$CH=C(CH$_3$)$_2$), 38.7 (CCH$_2$*C*H$_2$N(phthaloyl)), 23.88

($CCH_2CH=C(CH_3)_2$), 23.86 ($CCH_2CH_2N$(phthaloyl)), 25.6 ($CCH_2CH=C(CH_3)_2$), 25.5 ($NCH_2CH=C(CH_3)_2$), 18.1 ($NCH_2CH=C(CH_3)_2$), 18.0 ($CCH_2CH=C(CH_3)_2$).

**IR** (ATR): $\tilde{\nu}$ = 3385 $cm^{-1}$ (w), 3055 (w), 3028 (w), 2973 (w), 2931 (w), 2913 (w), 2858 (w), 1765 (w), 1705 (s), 1613 (w), 1463 (m), 1444 (m), 1393 (s), 1365 (s), 1351 (s), 1284 (w), 1263 (w), 1188 (w), 1169 (w), 1122 (w), 1101 (m), 1017 (s), 920 (w), 862 (w), 799 (w), 719 (s), 687 (w), 587 (w), 555 (w).

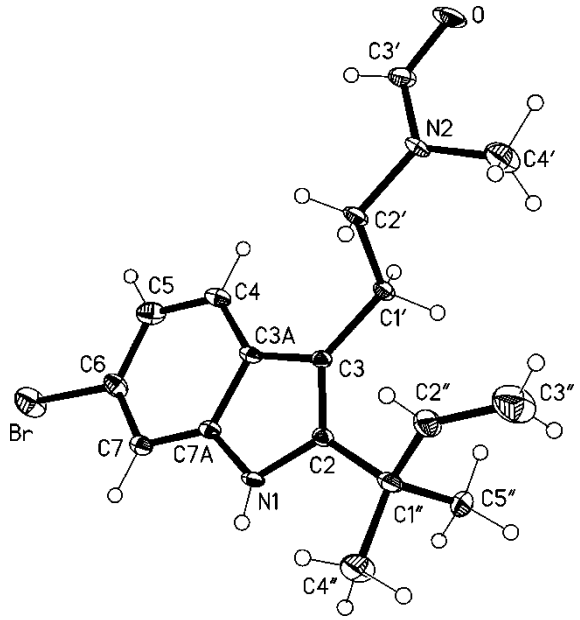
**UV** ($CHCl_3$): $\lambda_{max}$ (log ε) = 287 nm (3.97), 241 (4.34), 231 (3.88).

**MS** (ESI): *m/z* (%) = 875 $[2M+Na]^+$ (29), 450 (30), 449 $[M+Na]^+$ (100), 427 $[M+H]^+$ (34), 359 (5), 257 (5), 256 (29).

| | | |
|---|---|---|
| **HRMS** (ESI): | calcd. for $C_{28}H_{30}N_2O_2$ $[M+Na]^+$ | 449.2199, |
| | found | 449.2194. |

# 5 Crystallographic data

## 5.1 Crystallographic data of 1




Identification code: wobrom; Empirical formula: $C_{17}H_{21}BrN_2O$; $M_r$ = 349.27; Temperature: 100(2) K; Wavelength (λ) = 0.71073 Å; Crystal system: Orthorhombic; Space group: $P_{bca}$; a = 14.2247(10) Å, α = 90°, b = 10.8444(5) Å, β = 90°, c = 21.2757(9) Å, γ = 90°, Volume: 3282.0(3) $Å^3$ ; Z: 8; $\rho_{calc}$: 1.414 $Mg/m^3$; Absorption coefficient (μ) = 2.506 $mm^{-1}$; F(000): 1440; Crystal size: 0.40 x 0.25 x 0.15 $mm^3$; Theta range for data collection: 2.39 to 26.37°; Index ranges: -17<=h<=17, -13<=k<=13, 26<=l<=26; Reflections collected: 28293; Independent reflections: 3350 [R(int) = 0.0462] ; Final R indices [I>2 σ (I)]: R1 = 0.0455, wR2 = 0.1185; R indices (all data): R1 = 0.0771, wR2 = 0.1248; Largest diff. peak and hole:1.130 and -1.010 $e.Å^{-3}$;

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 6132(2) | 9628(3) | 2855.6(13) | 20.2(7) |
| C(2) | 5861(2) | 8622(3) | 3212.3(14) | 19.0(8) |
| C(3) | 5917(2) | 7583(3) | 2849.8(14) | 18.7(7) |

| | | | | |
|---|---|---|---|---|
| C(3A) | 6229(2) | 7958(3) | 2239.7(14) | 18.4(7) |
| C(4) | 6428(2) | 7349(3) | 1674.8(15) | 26.5(8) |
| C(5) | 6737(3) | 8009(3) | 1156.9(16) | 31.7(9) |
| C(6) | 6826(3) | 9291(3) | 1202.7(15) | 27.4(9) |
| C(7) | 6648(2) | 9943(3) | 1740.9(15) | 21.9(8) |
| C(7A) | 6351(2) | 9255(3) | 2259.1(14) | 17.5(7) |
| N(2) | 6315(2) | 4196(2) | 3259.0(13) | 25.9(7) |
| O | 6303.7(19) | 2188(2) | 2959.0(12) | 41.4(7) |
| Br | 7214.2(4) | 10156.1(4) | 465.2(2) | 47.1(2) |
| C(1') | 5681(2) | 6271(3) | 3017.5(15) | 21.7(8) |
| C(2') | 6548(2) | 5471(3) | 3108.4(17) | 26.5(9) |
| C(3') | 6465(3) | 3277(3) | 2858.3(18) | 32.2(9) |
| C(4') | 5885(3) | 3929(4) | 3873.0(16) | 46.3(12) |
| C(1") | 5527(3) | 8797(3) | 3885.1(16) | 31.2(9) |
| C(2") | 5878(7) | 7801(6) | 4298(3) | 36.1(18) |
| C(3") | 5350(6) | 7084(6) | 4651(3) | 64(3) |
| C(4") | 5788(13) | 10050(8) | 4147(8) | 39(4) |
| C(5") | 4421(4) | 8706(7) | 3851(4) | 38.2(18) |
| C(2") | 6229(11) | 8100(15) | 4305(8) | 41(5) |
| C(3") | 6964(9) | 7614(13) | 4278(6) | 52(5) |
| C(4") | 5660(20) | 10152(14) | 4075(18) | 28(7) |
| C(5") | 4567(11) | 8380(20) | 4065(11) | 90(9) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(7A) | 1.368(4) | C(6)-Br | 1.910(3) |
| N(1)-C(2) | 1.383(4) | C(7)-C(7A) | 1.396(4) |
| C(2)-C(3) | 1.368(4) | N(2)-C(3') | 1.328(4) |
| C(2)-C(1") | 1.520(4) | N(2)-C(2') | 1.457(4) |
| C(3)-C(3A) | 1.431(4) | N(2)-C(4') | 1.471(4) |
| C(3)-C(1') | 1.505(4) | O-C(3') | 1.222(4) |
| C(3A)-C(4) | 1.401(4) | C(1')-C(2') | 1.521(5) |
| C(3A)-C(7A) | 1.418(4) | C(1")-C(2") | 1.479(6) |
| C(4)-C(5) | 1.386(5) | C(1")-C(4") | 1.515(8) |
| C(5)-C(6) | 1.400(5) | C(1")-C(5") | 1.579(7) |
| C(6)-C(7) | 1.369(4) | C(2")-C(3") | 1.316(9) |

Table 3. Bond angles [°]

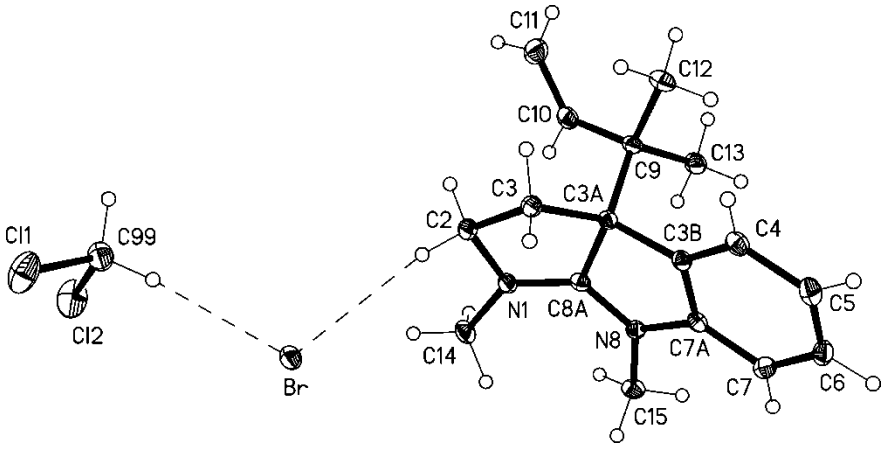
| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(7A)-N(1)-C(2) | 109.9(3) | C(3)-C(2)-C(1") | 130.7(3) |
| C(3)-C(2)-N(1) | 108.9(3) | N(1)-C(2)-C(1") | 120.4(3) |

| | | | |
|---|---|---|---|
| C(2)-C(3)-C(3A) | 107.2(3) | C(7)-C(7A)-C(3A) | 122.9(3) |
| C(2)-C(3)-C(1') | 129.2(3) | C(3')-N(2)-C(2') | 122.2(3) |
| C(3A)-C(3)-C(1') | 123.6(3) | C(3')-N(2)-C(4') | 119.3(3) |
| C(4)-C(3A)-C(7A) | 117.9(3) | C(2')-N(2)-C(4') | 118.5(3) |
| C(4)-C(3A)-C(3) | 135.0(3) | C(3)-C(1')-C(2') | 112.8(3) |
| C(7A)-C(3A)-C(3) | 107.1(3) | N(2)-C(2')-C(1') | 112.6(3) |
| C(5)-C(4)-C(3A) | 120.2(3) | O-C(3')-N(2) | 125.6(4) |
| C(4)-C(5)-C(6) | 119.1(3) | C(2")-C(1")-C(4") | 110.8(7) |
| C(7)-C(6)-C(5) | 123.7(3) | C(2")-C(1")-C(2) | 111.3(4) |
| C(7)-C(6)-Br | 119.1(3) | C(4")-C(1")-C(2) | 112.4(7) |
| C(5)-C(6)-Br | 117.2(3) | C(2")-C(1")-C(5") | 108.6(5) |
| C(6)-C(7)-C(7A) | 116.1(3) | C(4")-C(1")-C(5") | 108.5(7) |
| N(1)-C(7A)-C(7) | 130.1(3) | C(2)-C(1")-C(5") | 105.1(4) |
| N(1)-C(7A)-C(3A) | 107.0(3) | C(3")-C(2")-C(1") | 125.3(8) |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(01)...O#1 | 0.74(3) | 2.09(3) | 2.796(4) | 159(3) |

## 5.2 Crystallographic data of 13




Identification code: lada; Empirical formula: $C_{18}H_{25}BrCl_2N_2$; $M_r$ = 420.21; Temperature: 100(2) K; Wavelength (λ) = 0.71073 Å; Crystal system: Triclinic; Space group: P(-1); a = 7.7560(3) Å, α = 73.847(4)°, b = 10.4033(4) Å, = 78.274(4)°, c = 12.9292(6) Å, γ = 72.065(4)°, Volume: 945.43(7) $Å^3$; Z: 2; $\rho_{calc}$: 1.476 $Mg/m^3$;

Absorption coefficient (μ) = 2.458 $mm^{-1}$; F(000): 432; Crystal size: 0.30 x 0.20 x 0.15 $mm^3$; Theta range for data collection: 2.36 to 30.03°; Index ranges: -10<=h<=10, -14<=k<=14, -17<=l<=18; Reflections collected: 58212; Independent reflections: 5457 [R(int) = 0.0300]; Final R indices [I>2sigma(I)]: R1 = 0.0207, wR2 = 0.0511; R indices (all data): R1 = 0.0263, wR2 = 0.0516; Largest diff. peak and hole: 0.675 and -0.601 e.$Å^{-3}$;

Table 1. Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 3556.3(14) | 3790.6(10) | 3098.4(8) | 12.9(2) |
| C(2) | 5067.3(16) | 3706.1(13) | 2179.3(10) | 14.1(2) |
| C(3) | 5631.9(16) | 2166.3(13) | 2133.2(10) | 13.4(2) |
| C(3A) | 3884.0(15) | 1682.4(12) | 2634.8(9) | 10.9(2) |
| C(3B) | 3920.3(16) | 307.5(12) | 3450.4(10) | 11.9(2) |
| C(4) | 4746.7(16) | -1062.3(13) | 3409.5(10) | 14.7(2) |
| C(5) | 4330.3(17) | -2113.2(13) | 4280.1(11) | 17.0(3) |
| C(6) | 3101.0(17) | -1799.6(13) | 5176.5(10) | 16.6(3) |
| C(7) | 2279.4(16) | -420.7(13) | 5243.1(10) | 14.7(2) |
| C(7A) | 2715.0(16) | 602.3(12) | 4375.4(10) | 11.8(2) |
| N(8) | 2097.4(13) | 2066.9(10) | 4288.0(8) | 11.6(2) |
| C(8A) | 3022.2(15) | 2655.4(12) | 3385.2(9) | 11.0(2) |
| C(9) | 2613.4(16) | 1891.6(13) | 1733.3(10) | 12.5(2) |
| C(10) | 2181.1(16) | 3377.5(13) | 1071.0(10) | 15.3(2) |
| C(11) | 2573.3(18) | 3804.4(15) | 7.5(11) | 21.4(3) |
| C(12) | 3584.9(17) | 851.0(14) | 1025.0(10) | 17.1(3) |
| C(13) | 755.0(17) | 1613.9(14) | 2265.1(10) | 16.8(3) |
| C(14) | 3005.7(18) | 4957.4(13) | 3625.9(11) | 17.6(3) |
| C(15) | 967.6(17) | 2681.5(13) | 5175.8(10) | 15.2(2) |
| Br | 8194.0(2) | 5221.4(1) | 3119.4(1) | 15.6(1) |
| C(99) | 10217.1(19) | 7658.7(15) | 1026.5(12) | 22.5(3) |
| Cl(1) | 12604.8(5) | 7327.4(4) | 968.4(3) | 32.7(1) |
| Cl(2) | 9037.7(5) | 9212.2(4) | 1440.8(3) | 33.6(1) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(8A) | 1.3035(15) | C(3)-C(3A) | 1.5469(16) |
| N(1)-C(14) | 1.4642(15) | C(3A)-C(8A) | 1.5096(16) |
| N(1)-C(2) | 1.4906(15) | C(3A)-C(3B) | 1.5187(16) |
| C(2)-C(3) | 1.5402(17) | C(3A)-C(9) | 1.6034(16) |

| | | | |
|---|---|---|---|
| C(3B)-C(4) | 1.3820(16) | N(8)-C(15) | 1.4659(14) |
| C(3B)-C(7A) | 1.4041(16) | C(9)-C(10) | 1.5154(17) |
| C(4)-C(5) | 1.3971(18) | C(9)-C(12) | 1.5320(16) |
| C(5)-C(6) | 1.3887(18) | C(9)-C(13) | 1.5418(17) |
| C(6)-C(7) | 1.3982(18) | C(10)-C(11) | 1.3243(18) |
| C(7)-C(7A) | 1.3814(17) | C(99)-Cl(2) | 1.7628(14) |
| C(7A)-N(8) | 1.4285(15) | C(99)-Cl(1) | 1.7660(14) |
| N(8)-C(8A) | 1.3358(15) | | |

Table 3. Bond angles [°]

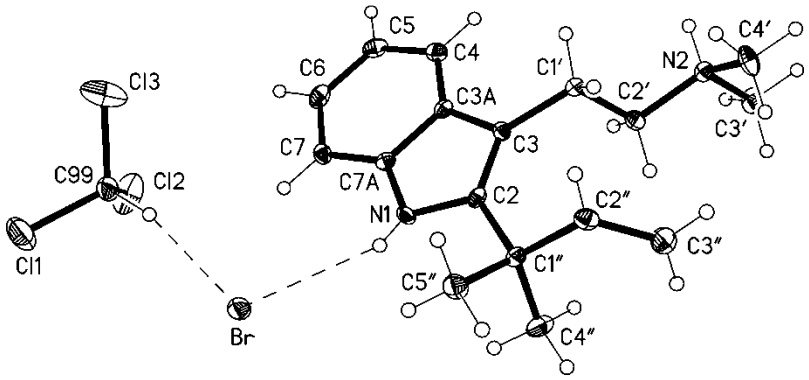
| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(8A)-N(1)-C(14) | 128.64(10) | C(7)-C(7A)-C(3B) | 122.84(11) |
| C(8A)-N(1)-C(2) | 110.10(10) | C(7)-C(7A)-N(8) | 126.74(11) |
| C(14)-N(1)-C(2) | 120.89(10) | C(3B)-C(7A)-N(8) | 110.38(10) |
| N(1)-C(2)-C(3) | 103.76(9) | C(8A)-N(8)-C(7A) | 106.77(9) |
| C(2)-C(3)-C(3A) | 103.80(9) | C(8A)-N(8)-C(15) | 129.21(10) |
| C(8A)-C(3A)-C(3B) | 99.22(9) | C(7A)-N(8)-C(15) | 122.78(10) |
| C(8A)-C(3A)-C(3) | 99.82(9) | N(1)-C(8A)-N(8) | 133.25(11) |
| C(3B)-C(3A)-C(3) | 122.60(10) | N(1)-C(8A)-C(3A) | 113.71(10) |
| C(8A)-C(3A)-C(9) | 112.07(9) | N(8)-C(8A)-C(3A) | 112.08(10) |
| C(3B)-C(3A)-C(9) | 109.74(9) | C(10)-C(9)-C(12) | 112.18(10) |
| C(3)-C(3A)-C(9) | 111.92(9) | C(10)-C(9)-C(13) | 105.90(10) |
| C(4)-C(3B)-C(7A) | 119.03(11) | C(12)-C(9)-C(13) | 108.50(10) |
| C(4)-C(3B)-C(3A) | 133.54(11) | C(10)-C(9)-C(3A) | 111.01(10) |
| C(7A)-C(3B)-C(3A) | 107.22(10) | C(12)-C(9)-C(3A) | 108.24(9) |
| C(3B)-C(4)-C(5) | 119.05(12) | C(13)-C(9)-C(3A) | 111.01(9) |
| C(6)-C(5)-C(4) | 121.02(12) | C(11)-C(10)-C(9) | 126.89(12) |
| C(5)-C(6)-C(7) | 120.78(12) | Cl(2)-C(99)-Cl(1) | 111.52(8) |
| C(7A)-C(7)-C(6) | 117.25(12) | | |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(2)-H(2A)...Br | 0.99 | 2.85 | 3.8029(12) | 162.5 |
| C(5)-H(5)...Br#1 | 0.95 | 3.01 | 3.7803(13) | 139.7 |
| C(6)-H(6)...Br#2 | 0.95 | 3.03 | 3.9337(13) | 159.1 |
| C(13)-H(13A)...Br#3 | 0.98 | 3.11 | 4.0093(13) | 152.5 |
| C(14)-H(14A)...Br#3 | 0.98 | 3.07 | 3.8332(13) | 136.2 |
| C(15)-H(15A)...Br#4 | 0.98 | 3.07 | 3.7647(13) | 129.4 |
| C(15)-H(15C)...Br#3 | 0.98 | 2.93 | 3.6870(13) | 135.3 |
| C(99)-H(99B)...Br | 0.99 | 2.65 | 3.6222(14) | 167.2 |
| C(2)-H(2B)...Cl(1)#3 | 0.99 | 3.00 | 3.7140(13) | 130.3 |

| | | | | |
|---|---|---|---|---|
| C(3)-H(3B)...Cl(1)#5 | 0.99 | 2.96 | 3.9074(13) | 160.3 |
| C(4)-H(4)...Cl(2)#1 | 0.95 | 2.99 | 3.7913(13) | 142.6 |

## 5.3 Crystallographic data of 20




Identification code: larder; Empirical formula: $C_{18}H_{25}DBrCl_3N_2$; $M_r$ = 457.68; Temperature: 100(2) K; Wavelength (λ) = 0.71073 Å; Crystal system: Monoclinic; Space group: $P2_{1/n}$; a = 9.2879(3) Å; α = 90°, b = 22.6454(6) Å, β = 105.571(4)°, c = 10.3652(3) Å; γ = 90°, Volume: 2100.08(11) $Å^3$; Z: 4; $\rho_{calc}$: 1.444 $Mg/m^3$; Absorption coefficient (μ) = 2.342 $mm^{-1}$; F(000): 936; Crystal size: 0.4 x 0.2 x 0.1 $mm^3$; Theta range for data collection 2.23 to 28.28°; Index ranges: -12<=h<=12, -30<=k<=30, -13<=l<=13; Reflections collected: 68893; Independent reflections: 5197 [R(int) = 0.0566]; Final R indices [I>2sigma(I)] R1 = 0.0280, wR2 = 0.0613 R indices (all data): R1 = 0.0436, wR2 = 0.0627; Largest diff. peak and hole: 0.735 and -0.469 e.$Å^{-3}$;

Table 1. Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 6962.5(18) | 2245.2(7) | 4956.4(17) | 11.6(4) |
| C(2) | 7362(2) | 2677.8(8) | 5937.2(19) | 11.0(4) |
| C(3) | 7472(2) | 2423.7(8) | 7163.2(18) | 10.5(4) |
| C(3A) | 7134(2) | 1803.2(8) | 6930.6(19) | 10.5(4) |
| C(4) | 7055(2) | 1323.4(9) | 7759(2) | 14.7(4) |
| C(5) | 6750(2) | 771.0(9) | 7191(2) | 16.1(4) |

| | | | | |
|---|---|---|---|---|
| C(6) | 6513(2) | 682.9(9) | 5809(2) | 16.8(4) |
| C(7) | 6555(2) | 1149.4(8) | 4961(2) | 13.1(4) |
| C(7A) | 6847(2) | 1708.4(8) | 5532.7(19) | 10.9(4) |
| N(2) | 6805.3(18) | 3166.2(7) | 10286.8(16) | 11.9(4) |
| C(1') | 7860(2) | 2694.4(8) | 8541.2(19) | 11.6(4) |
| C(2') | 6495(2) | 2969.6(8) | 8854.4(19) | 13.6(4) |
| C(3') | 5404(2) | 3359.2(9) | 10600(2) | 19.4(5) |
| C(4') | 7973(2) | 3634.6(9) | 10653(2) | 18.8(5) |
| C(1'') | 7460(2) | 3312.5(8) | 5485.9(19) | 12.7(4) |
| C(2'') | 8292(2) | 3690.0(8) | 6647.4(19) | 14.7(4) |
| C(3'') | 7766(2) | 4150.5(9) | 7152(2) | 20.3(5) |
| C(4'') | 5867(2) | 3532.7(9) | 4844(2) | 19.2(5) |
| C(5'') | 8373(2) | 3344.1(9) | 4440.8(19) | 17.8(5) |
| Br | 7474.1(2) | 1945.3(1) | 1896.7(2) | 17.1(1) |
| C(99) | 7948(2) | 370.2(9) | 2057(2) | 20.0(5) |
| Cl(1) | 8323.3(8) | 250.8(3) | 517.2(6) | 36.9(2) |
| Cl(2) | 6296.1(7) | 16.1(3) | 2141.1(7) | 40.4(2) |
| Cl(3) | 9447.6(8) | 120.3(3) | 3361.3(6) | 46.4(2) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(7A) | 1.371(2) | N(2)-C(3') | 1.489(2) |
| N(1)-C(2) | 1.389(2) | N(2)-C(4') | 1.491(2) |
| C(2)-C(3) | 1.374(3) | N(2)-C(2') | 1.502(2) |
| C(2)-C(1'') | 1.522(3) | C(1')-C(2') | 1.523(3) |
| C(3)-C(3A) | 1.446(3) | C(1'')-C(2'') | 1.509(3) |
| C(3)-C(1') | 1.506(3) | C(1'')-C(4'') | 1.534(3) |
| C(3A)-C(4) | 1.399(3) | C(1'')-C(5'') | 1.546(3) |
| C(3A)-C(7A) | 1.418(3) | C(2'')-C(3'') | 1.318(3) |
| C(4)-C(5) | 1.379(3) | C(99)-Cl(1) | 1.744(2) |
| C(5)-C(6) | 1.404(3) | C(99)-Cl(3) | 1.754(2) |
| C(6)-C(7) | 1.381(3) | C(99)-Cl(2) | 1.754(2) |
| C(7)-C(7A) | 1.393(3) | | |

Table 3. Bond angles [°]

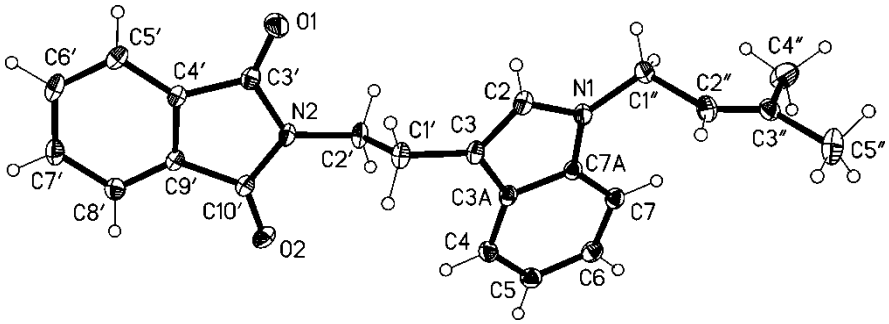
| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(7A)-N(1)-C(2) | 110.07(16) | C(2)-C(3)-C(1') | 130.26(18) |
| C(3)-C(2)-N(1) | 108.71(16) | C(3A)-C(3)-C(1') | 122.65(16) |
| C(3)-C(2)-C(1'') | 133.18(17) | C(4)-C(3A)-C(7A) | 118.90(17) |
| N(1)-C(2)-C(1'') | 117.87(16) | C(4)-C(3A)-C(3) | 134.22(18) |
| C(2)-C(3)-C(3A) | 107.09(16) | C(7A)-C(3A)-C(3) | 106.88(16) |

| | | | |
|---|---|---|---|
| C(5)-C(4)-C(3A) | 118.76(18) | N(2)-C(2')-C(1') | 112.47(15) |
| C(4)-C(5)-C(6) | 121.50(18) | C(2")-C(1")-C(2) | 110.48(16) |
| C(7)-C(6)-C(5) | 121.11(18) | C(2")-C(1")-C(4") | 112.94(16) |
| C(6)-C(7)-C(7A) | 117.41(18) | C(2)-C(1")-C(4") | 108.05(16) |
| N(1)-C(7A)-C(7) | 130.50(17) | C(2")-C(1")-C(5") | 105.85(15) |
| N(1)-C(7A)-C(3A) | 107.21(16) | C(2)-C(1")-C(5") | 110.40(15) |
| C(7)-C(7A)-C(3A) | 122.27(17) | C(4")-C(1")-C(5") | 109.12(16) |
| C(3')-N(2)-C(4') | 110.75(15) | C(3")-C(2")-C(1") | 126.84(19) |
| C(3')-N(2)-C(2') | 110.84(15) | Cl(1)-C(99)-Cl(3) | 110.07(12) |
| C(4')-N(2)-C(2') | 113.31(15) | Cl(1)-C(99)-Cl(2) | 111.51(12) |
| C(3)-C(1')-C(2') | 111.57(16) | Cl(3)-C(99)-Cl(2) | 109.79(11) |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(01)...Br | 0.806(16) | 2.653(17) | 3.3991(17) | 154.7(17) |
| N(2)-H(02)...Br#1 | 0.855(17) | 2.360(17) | 3.2027(17) | 169.0(19) |
| C(99)-H(99)...Br | 1.00 | 2.61 | 3.593(2) | 167.1 |
| C(2')-H(2'2)...Br#2 | 0.99 | 3.16 | 3.7463(19) | 119.4 |
| C(5")-H(5"1)...Br#3 | 0.98 | 3.09 | 4.027(2) | 159.8 |
| C(5")-H(5"3)...Br | 0.98 | 3.15 | 4.062(2) | 155.2 |

## 5.4 Crystallographic data of 208




Identification code: sachin; Empirical formula : $C_{23}H_{22}N_2O_2$; $M_r$ = 358.43; Temperature: 100(2) K; Wavelength (λ) = 0.71073 Å; Crystal system: Monoclinic; Space group: $P2_{1/n}$; a = 4.99523(13) Å; α = 90°, b = 22.8077(6) Å, β = 92.333(3)°, c = 16.2552(5) Å; γ = 90°, Volume: 1850.42(9) Å$^3$; Z: 4; $\rho_{calc}$ : 1.287

$Mg/m^3$; Absorption coefficient (μ) = 0.083 $mm^{-1}$; F(000): 760; Crystal size: 0.4 x 0.15 x 0.15 $mm^3$; Theta range for data collection: 2.51 to 30.03°; Index ranges: -7<=h<=7, -31<=k<=31, -22<=l<=22; Reflections collected: 67554; Independent reflections: 5354 [R(int) = 0.0306]; Final R indices [I>2sigma(I)] R1 = 0.0416, wR2 = 0.1049; R indices (all data) R1 = 0.0482, wR2 = 0.1091; Largest diff. peak and hole = 0.354 and -0.246 e.$Å^{-3}$.

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 8144.5(17) | 4869.8(4) | 2622.9(5) | 16.1(2) |
| C(2) | 7772(2) | 4980.4(4) | 3445.1(6) | 17.5(2) |
| C(3) | 5782(2) | 5388.7(4) | 3530.5(6) | 16.3(2) |
| C(3A) | 4850.3(19) | 5541.2(4) | 2710.0(6) | 15.0(2) |
| C(4) | 2850(2) | 5917.2(4) | 2385.7(6) | 17.7(2) |
| C(5) | 2477(2) | 5964.4(5) | 1540.1(6) | 19.9(2) |
| C(6) | 4081(2) | 5644.4(5) | 1006.2(6) | 19.8(2) |
| C(7) | 6052(2) | 5263.9(4) | 1305.5(6) | 17.5(2) |
| C(7A) | 6397.2(19) | 5213.1(4) | 2160.8(6) | 14.7(2) |
| N(2) | 5304.5(17) | 6618.1(4) | 5086.4(5) | 16.2(2) |
| O(1) | 8792.4(16) | 6270.7(4) | 5928.5(5) | 23.7(2) |
| O(2) | 1592.8(16) | 7131.1(4) | 4584.6(5) | 21.9(2) |
| C(1') | 4945(2) | 5676.4(4) | 4308.0(6) | 18.3(2) |
| C(2') | 5966(2) | 6308.2(4) | 4338.7(6) | 18.0(2) |
| C(3') | 6862(2) | 6586.2(4) | 5819.0(6) | 16.6(2) |
| C(4') | 5670.7(19) | 7016.8(4) | 6389.2(6) | 15.2(2) |
| C(5') | 6453(2) | 7175.8(5) | 7184.2(6) | 19.1(2) |
| C(6') | 5003(2) | 7623.3(5) | 7550.5(6) | 21.2(2) |
| C(7') | 2866(2) | 7895.5(5) | 7130.5(6) | 21.4(2) |
| C(8') | 2071(2) | 7728.6(5) | 6329.0(6) | 19.3(2) |
| C(9') | 3515.1(19) | 7285.3(4) | 5973.7(6) | 15.0(2) |
| C(10') | 3223(2) | 7022.3(4) | 5136.4(6) | 15.4(2) |
| C(1'') | 10120(2) | 4471.9(4) | 2292.1(6) | 18.1(2) |
| C(2'') | 8832(2) | 3951.6(4) | 1872.8(6) | 19.7(2) |
| C(3'') | 9487(2) | 3723.7(5) | 1152.7(6) | 19.2(2) |
| C(4'') | 11619(2) | 3969.8(7) | 628.4(8) | 35.7(3) |
| C(5'') | 8142(3) | 3180.3(5) | 812.9(8) | 32.3(3) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(7A) | 1.3731(12) | O(1)-C(3') | 1.2105(13) |
| N(1)-C(2) | 1.3801(12) | O(2)-C(10') | 1.2124(12) |
| N(1)-C(1") | 1.4594(12) | C(1')-C(2') | 1.5287(14) |
| C(2)-C(3) | 1.3733(14) | C(3')-C(4') | 1.4909(13) |
| C(3)-C(3A) | 1.4375(13) | C(4')-C(5') | 1.3833(13) |
| C(3)-C(1') | 1.4985(13) | C(4')-C(9') | 1.3897(13) |
| C(3A)-C(4) | 1.4031(14) | C(5')-C(6') | 1.3986(15) |
| C(3A)-C(7A) | 1.4177(13) | C(6')-C(7') | 1.3898(16) |
| C(4)-C(5) | 1.3838(14) | C(7')-C(8') | 1.3991(14) |
| C(5)-C(6) | 1.4089(15) | C(8')-C(9') | 1.3820(14) |
| C(6)-C(7) | 1.3856(14) | C(9')-C(10') | 1.4891(13) |
| C(7)-C(7A) | 1.3989(13) | C(1")-C(2") | 1.5003(14) |
| N(2)-C(10') | 1.3942(13) | C(2")-C(3") | 1.3336(14) |
| N(2)-C(3') | 1.3975(12) | C(3")-C(4") | 1.4997(16) |
| N(2)-C(2') | 1.4557(12) | C(3")-C(5") | 1.5042(16) |

Table 3. Bond angles [°]

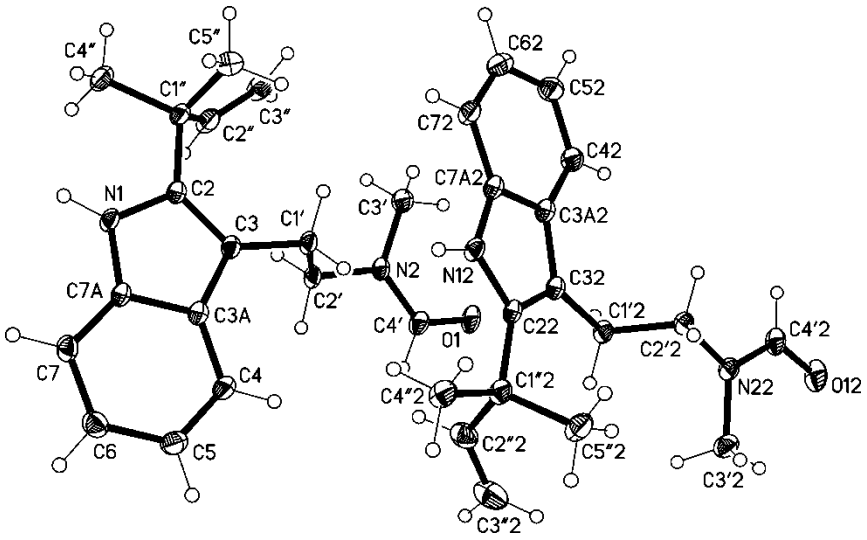
| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(7A)-N(1)-C(2) | 108.53(8) | C(3)-C(1')-C(2') | 109.64(8) |
| C(7A)-N(1)-C(1") | 125.26(8) | N(2)-C(2')-C(1') | 113.46(8) |
| C(2)-N(1)-C(1") | 126.17(8) | O(1)-C(3')-N(2) | 124.67(9) |
| C(3)-C(2)-N(1) | 110.39(9) | O(1)-C(3')-C(4') | 129.48(9) |
| C(2)-C(3)-C(3A) | 106.18(8) | N(2)-C(3')-C(4') | 105.84(8) |
| C(2)-C(3)-C(1') | 127.60(9) | C(5')-C(4')-C(9') | 121.50(9) |
| C(3A)-C(3)-C(1') | 125.86(9) | C(5')-C(4')-C(3') | 130.45(9) |
| C(4)-C(3A)-C(7A) | 118.96(9) | C(9')-C(4')-C(3') | 108.00(8) |
| C(4)-C(3A)-C(3) | 134.04(9) | C(4')-C(5')-C(6') | 117.22(9) |
| C(7A)-C(3A)-C(3) | 107.00(8) | C(7')-C(6')-C(5') | 121.18(9) |
| C(5)-C(4)-C(3A) | 119.07(9) | C(6')-C(7')-C(8') | 121.26(10) |
| C(4)-C(5)-C(6) | 120.96(9) | C(9')-C(8')-C(7') | 117.08(10) |
| C(7)-C(6)-C(5) | 121.47(9) | C(8')-C(9')-C(4') | 121.76(9) |
| C(6)-C(7)-C(7A) | 117.25(9) | C(8')-C(9')-C(10') | 130.05(9) |
| N(1)-C(7A)-C(7) | 129.85(9) | C(4')-C(9')-C(10') | 108.17(8) |
| N(1)-C(7A)-C(3A) | 107.89(8) | O(2)-C(10')-N(2) | 124.91(9) |
| C(7)-C(7A)-C(3A) | 122.26(9) | O(2)-C(10')-C(9') | 129.16(9) |
| C(10')-N(2)-C(3') | 112.05(8) | N(2)-C(10')-C(9') | 105.91(8) |
| C(10')-N(2)-C(2') | 124.39(8) | N(1)-C(1")-C(2") | 112.05(8) |
| C(3')-N(2)-C(2') | 123.28(9) | C(3")-C(2")-C(1") | 126.23(10) |

| | | | |
|---|---|---|---|
| C(2")-C(3")-C(4") | 123.93(10) | C(4")-C(3")-C(5") | 114.63(10) |
| C(2")-C(3")-C(5") | 121.43(10) | | |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(1")-H(1"1)...O(1)#1 | 0.99 | 2.56 | 3.3766(13) | 139.5 |
| C(2')-H(2'1)...O(2)#2 | 0.99 | 2.65 | 3.3897(13) | 131.5 |
| C(6')-H(6')...O(2)#3 | 0.95 | 2.48 | 3.4153(12) | 169.6 |

## 5.5 Crystallographic data of 2




Identification code : flust; Empirical formula: $C_{17}H_{22}N_2O$; $M_r$ = 270.37; Temperature: 100(2) K; Wavelength (λ) = 1.54184 Å; Crystal system: Monoclinic; Space group: Cc; a = 21.5126(8) Å; α = 90°, b = 14.3444(4) Å, β = 114.685(4)°, c = 10.8812(4) Å; γ = 90°, Volume: 3050.95(17) $Å^3$; Z: 8; $\rho_{calc}$: 1.177 $Mg/m^3$; Absorption coefficient (μ) = 0.575 $mm^{-1}$; F(000): 1168 ; Crystal size: 0.20 x 0.08 x 0.03 $mm^3$; Theta range for data collection: 3.82 to 76.26°; Index ranges: -27<=h<=26, -18<=k<=18, -13<=l<=11; Reflections collected: 28569; Independent reflections: 3190 [R(int) = 0.0373]; Final R indices [I>2sigma(I)] R1 = 0.0358, wR2 = 0.0975; R indices (all data) R1 = 0.0372, wR2 = 0.0990; Largest diff. peak and hole = 0.266 and -0.183 e.$Å^{-3}$.

Table 1. Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 2432.5(9) | 1270.4(12) | -2399.9(17) | 26.1(3) |
| C(2) | 2815.0(11) | 1529.1(14) | -1070(2) | 26.0(4) |
| C(3) | 2396.0(11) | 1556.4(14) | -399(2) | 25.7(4) |
| C(3A) | 1723.1(11) | 1300.1(14) | -1358(2) | 26.1(4) |
| C(4) | 1085.3(11) | 1189.8(16) | -1305(2) | 30.9(4) |
| C(5) | 525.2(12) | 931.7(18) | -2465(2) | 36.0(5) |
| C(6) | 582.0(12) | 767.4(17) | -3688(2) | 35.1(5) |
| C(7) | 1203.4(12) | 861.4(15) | -3777(2) | 30.3(4) |
| C(7A) | 1765.9(11) | 1130.7(14) | -2602(2) | 25.5(4) |
| C(1') | 2575.8(11) | 1808.7(15) | 1054(2) | 26.9(4) |
| C(2') | 2667.0(11) | 944.5(14) | 1935(2) | 27.1(4) |
| C(3') | 3570.0(12) | 1555.9(18) | 4113(2) | 36.0(5) |
| C(4') | 2502.6(13) | 965.7(16) | 4038(2) | 31.2(4) |
| N(2) | 2890.0(10) | 1168.7(13) | 3376.8(17) | 28.6(4) |
| O(1) | 2674.0(10) | 1088.6(12) | 5245.0(17) | 38.6(4) |
| C(1'') | 3573.1(11) | 1736.7(17) | -560(2) | 30.8(4) |
| C(2'') | 3951.5(12) | 1165(2) | 707(2) | 39.0(5) |
| C(3'') | 4398.0(13) | 1462(3) | 1896(3) | 53.2(8) |
| C(4'') | 3852.3(13) | 1431(2) | -1594(3) | 42.4(6) |
| C(5'') | 3696.4(14) | 2789.3(19) | -323(3) | 44.9(6) |
| N(12) | 2008.1(9) | 3773.0(13) | 2083.7(17) | 25.8(3) |
| C(22) | 1642.4(11) | 3473.8(14) | 2798(2) | 25.2(4) |
| C(32) | 2073.1(11) | 3438.2(14) | 4157(2) | 25.8(4) |
| C(3A2) | 2733.4(11) | 3735.6(14) | 4289(2) | 27.0(4) |
| C(42) | 3369.9(12) | 3867.8(16) | 5382(2) | 32.8(5) |
| C(52) | 3916.5(12) | 4172.0(19) | 5141(3) | 39.1(5) |
| C(62) | 3847.6(12) | 4339.5(18) | 3813(3) | 38.5(5) |
| C(72) | 3229.8(12) | 4219.8(16) | 2713(2) | 32.3(4) |
| C(7A2) | 2676.5(11) | 3920.2(15) | 2967(2) | 26.5(4) |
| C(1'2) | 1909.2(11) | 3166.1(15) | 5325(2) | 27.1(4) |
| C(2'2) | 1828.8(11) | 4018.8(15) | 6085(2) | 27.6(4) |
| C(3'2) | 915.5(12) | 3441.7(18) | 6735(3) | 37.1(5) |
| C(4'2) | 1986.8(14) | 4002.1(16) | 8442(2) | 34.5(5) |
| N(22) | 1604.7(10) | 3792.9(13) | 7147.0(18) | 29.2(4) |
| O(12) | 1806.8(12) | 3890.5(13) | 9365.3(18) | 45.9(5) |
| C(1"2) | 888.6(11) | 3229.2(16) | 2066(2) | 30.4(4) |
| C(2"2) | 818.5(12) | 2191.8(19) | 2273(2) | 39.9(5) |
| C(3"2) | 439.8(17) | 1812(2) | 2835(3) | 56.5(8) |
| C(4"2) | 623.9(12) | 3390(2) | 531(2) | 37.9(5) |
| C(5"2) | 466.5(13) | 3843(2) | 2596(3) | 41.5(6) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(7A) | 1.372(3) | N(12)-C(7A2) | 1.372(3) |
| N(1)-C(2) | 1.384(3) | N(12)-C(22) | 1.385(3) |
| C(2)-C(3) | 1.377(3) | C(22)-C(32) | 1.380(3) |
| C(2)-C(1") | 1.517(3) | C(22)-C(1"2) | 1.519(3) |
| C(3)-C(3A) | 1.434(3) | C(32)-C(3A2) | 1.432(3) |
| C(3)-C(1') | 1.506(3) | C(32)-C(1'2) | 1.506(3) |
| C(3A)-C(4) | 1.406(3) | C(3A2)-C(42) | 1.402(3) |
| C(3A)-C(7A) | 1.416(3) | C(3A2)-C(7A2) | 1.416(3) |
| C(4)-C(5) | 1.383(3) | C(42)-C(52) | 1.378(3) |
| C(5)-C(6) | 1.406(3) | C(52)-C(62) | 1.411(3) |
| C(6)-C(7) | 1.386(3) | C(62)-C(72) | 1.379(3) |
| C(7)-C(7A) | 1.398(3) | C(72)-C(7A2) | 1.398(3) |
| C(1')-C(2') | 1.529(3) | C(1'2)-C(2'2) | 1.526(3) |
| C(2')-N(2) | 1.472(2) | C(2'2)-N(22) | 1.462(3) |
| C(3')-N(2) | 1.453(3) | C(3'2)-N(22) | 1.448(3) |
| C(4')-O(1) | 1.219(3) | C(4'2)-O(12) | 1.228(3) |
| C(4')-N(2) | 1.341(3) | C(4'2)-N(22) | 1.336(3) |
| C(1")-C(2") | 1.516(3) | C(1"2)-C(2"2) | 1.522(3) |
| C(1")-C(5") | 1.536(3) | C(1"2)-C(5"2) | 1.539(3) |
| C(1")-C(4") | 1.544(3) | C(1"2)-C(4"2) | 1.541(3) |
| C(2")-C(3") | 1.319(4) | C(2"2)-C(3"2) | 1.323(4) |

Table 3. Bond angles [°]

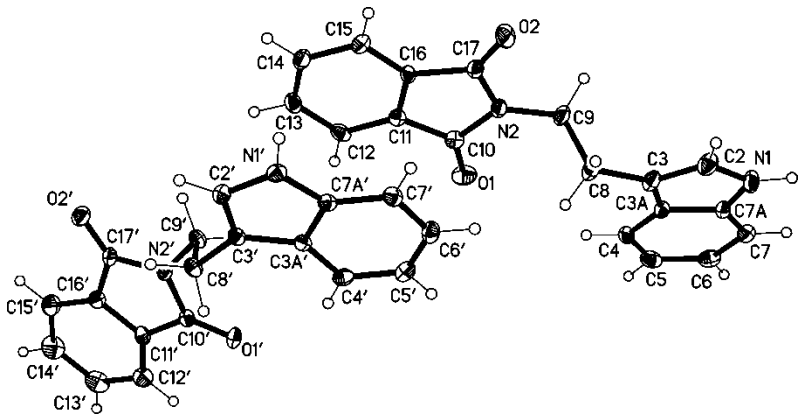
| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C C(7A)-N(1)-C(2) | 109.41(17) | N(1)-C(7A)-C(7) | 129.42(19) |
| C(3)-C(2)-N(1) | 109.08(18) | N(1)-C(7A)-C(3A) | 107.60(17) |
| C(3)-C(2)-C(1") | 130.00(19) | C(7)-C(7A)-C(3A) | 122.98(19) |
| N(1)-C(2)-C(1") | 120.92(18) | C(3)-C(1')-C(2') | 111.89(16) |
| C(2)-C(3)-C(3A) | 107.00(18) | N(2)-C(2')-C(1') | 112.99(17) |
| C(2)-C(3)-C(1') | 128.68(19) | O(1)-C(4')-N(2) | 124.8(2) |
| C(3A)-C(3)-C(1') | 124.32(18) | C(4')-N(2)-C(3') | 119.69(18) |
| C(4)-C(3A)-C(7A) | 118.32(19) | C(4')-N(2)-C(2') | 121.71(19) |
| C(4)-C(3A)-C(3) | 134.77(19) | C(3')-N(2)-C(2') | 118.43(18) |
| C(7A)-C(3A)-C(3) | 106.91(18) | C(2")-C(1")-C(2) | 108.25(18) |
| C(5)-C(4)-C(3A) | 119.0(2) | C(2")-C(1")-C(5") | 112.9(2) |
| C(4)-C(5)-C(6) | 121.5(2) | C(2)-C(1")-C(5") | 109.77(19) |
| C(7)-C(6)-C(5) | 121.1(2) | C(2")-C(1")-C(4") | 106.5(2) |
| C(6)-C(7)-C(7A) | 117.05(19) | C(2)-C(1")-C(4") | 111.35(18) |

| | | | |
|---|---|---|---|
| C(5")-C(1")-C(4") | 108.0(2) | N(12)-C(7A2)-C(72) | 129.7(2) |
| C(3")-C(2")-C(1") | 127.7(3) | N(12)-C(7A2)-C(3A2) | 107.69(18) |
| C(7A2)-N(12)-C(22) | 109.22(17) | C(72)-C(7A2)-C(3A2) | 122.6(2) |
| C(32)-C(22)-N(12) | 109.17(19) | C(32)-C(1'2)-C(2'2) | 111.67(17) |
| C(32)-C(22)-C(1"2) | 130.18(19) | N(22)-C(2'2)-C(1'2) | 113.57(17) |
| N(12)-C(22)-C(1"2) | 120.65(18) | O(12)-C(4'2)-N(22) | 124.6(3) |
| C(22)-C(32)-C(3A2) | 106.87(19) | C(4'2)-N(22)-C(3'2) | 120.3(2) |
| C(22)-C(32)-C(1'2) | 128.71(19) | C(4'2)-N(22)-C(2'2) | 121.55(19) |
| C(3A2)-C(32)-C(1'2) | 124.40(18) | C(3'2)-N(22)-C(2'2) | 117.73(18) |
| C(42)-C(3A2)-C(7A2) | 118.4(2) | C(22)-C(1"2)-C(2"2) | 107.35(18) |
| C(42)-C(3A2)-C(32) | 134.6(2) | C(22)-C(1"2)-C(5"2) | 109.82(18) |
| C(7A2)-C(3A2)-C(32) | 107.01(18) | C(2"2)-C(1"2)-C(5"2) | 113.2(2) |
| C(52)-C(42)-C(3A2) | 119.4(2) | C(22)-C(1"2)-C(4"2) | 111.34(19) |
| C(42)-C(52)-C(62) | 121.0(2) | C(2"2)-C(1"2)-C(4"2) | 107.01(19) |
| C(72)-C(62)-C(52) | 121.3(2) | C(5"2)-C(1"2)-C(4"2) | 108.2(2) |
| C(62)-C(72)-C(7A2) | 117.2(2) | C(3"2)-C(2"2)-C(1"2) | 126.1(3) |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(01)...O(1)#1 | 0.90(2) | 1.95(2) | 2.831(2) | 167(2) |
| N(12)-H(012)...O(12)#1 | 0.88(2) | 1.96(2) | 2.810(2) | 164(2) |

## 5.6 Crystallographic data of 165




Identification code: skaph ; Empirical formula: $C_{18}H_{14}N_2O_2$ ; $M_r$ = 290.31; Temperature: 100(2) K; Wavelength (λ) = 0.71073 Å; Crystal system: Monoclinic;

Space group: P21; a = 7.2013(2) Å; α = 90°, b = 12.9847(3) Å, β = 97.824(3)°, c = 15.1782(4) Å, γ = 90°, Volume: 1406.05(6) $Å^3$; Z: 4; $\rho_{calc}$: 1.371 $Mg/m^3$; Absorption coefficient (μ) = 0.091 $mm^{-1}$; F(000): 608; Crystal size: 0.40 x 0.25 x 0.08 $mm^3$; Theta range for data collection2.71 to 30.50°; Index ranges: -10<=h<=10, -18<=k<=18, -21<=l<=21; Reflections collected: 53966; Independent reflection: 4378 [R(int) = 0.0403]; Final R indices [I>2sigma(I)] R1 = 0.0362, wR2 = 0.0869; R indices (all data) R1 = 0.0421, wR2 = 0.0907; Largest diff. peak and hole = 0.335 and -0.233 $e.Å^{-3}$.

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | -344(2) | 6582.7(12) | 9872.8(10) | 22.2(3) |
| C(2) | 301(3) | 5613.4(15) | 9704.3(12) | 23.8(4) |
| C(3) | 525(2) | 5512.3(15) | 8826.5(12) | 20.3(3) |
| C(3A) | -4(2) | 6485.5(14) | 8423.0(11) | 16.5(3) |
| C(4) | -65(2) | 6883.1(15) | 7558.3(11) | 20.0(3) |
| C(5) | -583(3) | 7900.9(16) | 7401.3(12) | 23.4(4) |
| C(6) | -1099(3) | 8534.1(15) | 8084.6(12) | 22.6(4) |
| C(7) | -1087(2) | 8152.1(14) | 8935.3(12) | 20.0(3) |
| C(7A) | -516(2) | 7139.2(13) | 9097.9(10) | 16.5(3) |
| C(8) | 1139(3) | 4574.1(15) | 8371.5(13) | 24.2(4) |
| C(9) | -537(2) | 3992.8(14) | 7883.1(13) | 21.2(3) |
| N(2) | 15(2) | 3182.4(12) | 7303.3(9) | 17.1(3) |
| C(10) | 391(2) | 3367.4(14) | 6432.5(11) | 17.3(3) |
| O(1) | 372.6(19) | 4210.7(11) | 6095.5(10) | 25.2(3) |
| C(11) | 784(2) | 2345.6(13) | 6064.7(10) | 14.6(3) |
| C(12) | 1229(2) | 2075.5(15) | 5237.2(11) | 18.8(3) |
| C(13) | 1506(2) | 1030.6(16) | 5080.0(11) | 20.8(4) |
| C(14) | 1380(2) | 298.9(14) | 5737.5(12) | 20.2(3) |
| C(15) | 975(2) | 577.5(14) | 6579.3(11) | 17.3(3) |
| C(16) | 656(2) | 1609.1(13) | 6719.1(10) | 13.8(3) |
| C(17) | 201(2) | 2151.9(14) | 7527.0(11) | 16.3(3) |
| O(2) | 35(2) | 1786.2(11) | 8252.0(8) | 25.4(3) |
| N(1') | 6052(2) | 464.1(11) | 6271.4(9) | 16.2(3) |
| C(2') | 6442(2) | 351.0(13) | 5408.3(10) | 15.8(3) |
| C(3') | 6435(2) | 1288.8(13) | 4997.5(10) | 14.2(3) |
| C(3A') | 6003(2) | 2037.5(13) | 5636.8(10) | 13.3(3) |
| C(4') | 5807(2) | 3114.6(13) | 5622.1(11) | 16.9(3) |
| C(5') | 5336(2) | 3606.9(14) | 6371.6(12) | 19.6(3) |
| C(6') | 5069(2) | 3052.0(15) | 7137.5(11) | 19.5(3) |

| | | | | |
|---|---|---|---|---|
| C(7') | 5278(2) | 1990.5(14) | 7176.2(10) | 16.7(3) |
| C(7A') | 5750(2) | 1492.3(13) | 6419.5(10) | 14.1(3) |
| C(8') | 6769(2) | 1497.2(14) | 4059.6(10) | 16.3(3) |
| C(9') | 4925(2) | 1744.2(14) | 3462.8(10) | 15.8(3) |
| N(2') | 5224.2(19) | 2084.9(11) | 2578.5(9) | 14.5(3) |
| C(10') | 5643(2) | 3097.4(13) | 2382.5(11) | 15.2(3) |
| O(1') | 5804.6(18) | 3795.7(11) | 2918.7(8) | 21.9(3) |
| C(11') | 5812(2) | 3124.9(14) | 1417.5(10) | 16.0(3) |
| C(12') | 6215(3) | 3939.9(15) | 889.6(12) | 22.3(4) |
| C(13') | 6238(3) | 3732.5(17) | -14.5(12) | 28.1(4) |
| C(14') | 5888(3) | 2748.8(18) | -352.0(12) | 29.8(4) |
| C(15') | 5483(3) | 1932.2(16) | 185.7(11) | 23.4(4) |
| C(16') | 5450(2) | 2144.6(14) | 1075.6(10) | 16.1(3) |
| C(17') | 5056(2) | 1453.7(13) | 1819.2(10) | 15.2(3) |
| O(2') | 4660.3(18) | 550.2(10) | 1809.4(8) | 21.3(3) |

Table 2. Bond lengths [Å]

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| N(1)-C(7A) | 1.371(2) | C(16)-C(17) | 1.489(2) |
| N(1)-C(2) | 1.377(2) | C(17)-O(2) | 1.219(2) |
| C(2)-C(3) | 1.370(2) | N(1')-C(7A') | 1.376(2) |
| C(3)-C(3A) | 1.433(3) | N(1')-C(2') | 1.384(2) |
| C(3)-C(8) | 1.496(2) | C(2')-C(3') | 1.368(2) |
| C(3A)-C(4) | 1.405(2) | C(3')-C(3A') | 1.437(2) |
| C(3A)-C(7A) | 1.417(2) | C(3')-C(8') | 1.500(2) |
| C(4)-C(5) | 1.385(3) | C(3A')-C(4') | 1.406(2) |
| C(5)-C(6) | 1.412(3) | C(3A')-C(7A') | 1.416(2) |
| C(6)-C(7) | 1.382(3) | C(4')-C(5') | 1.387(2) |
| C(7)-C(7A) | 1.390(3) | C(5')-C(6') | 1.403(3) |
| C(8)-C(9) | 1.527(3) | C(6')-C(7') | 1.387(3) |
| C(9)-N(2) | 1.461(2) | C(7')-C(7A') | 1.400(2) |
| N(2)-C(17) | 1.383(2) | C(8')-C(9') | 1.536(2) |
| N(2)-C(10) | 1.406(2) | C(9')-N(2') | 1.457(2) |
| C(10)-O(1) | 1.208(2) | N(2')-C(10') | 1.390(2) |
| C(10)-C(11) | 1.481(2) | N(2')-C(17') | 1.406(2) |
| C(11)-C(12) | 1.383(2) | C(10')-O(1') | 1.213(2) |
| C(11)-C(16) | 1.391(2) | C(10')-C(11') | 1.487(2) |
| C(12)-C(13) | 1.397(3) | C(11')-C(12') | 1.382(2) |
| C(13)-C(14) | 1.390(3) | C(11')-C(16') | 1.386(2) |
| C(14)-C(15) | 1.396(2) | C(12')-C(13') | 1.401(3) |
| C(15)-C(16) | 1.380(2) | C(13')-C(14') | 1.387(3) |

| | | | |
|---|---|---|---|
| C(14')-C(15') | 1.393(3) | C(16')-C(17') | 1.499(2) |
| C(15')-C(16') | 1.382(2) | C(17')-O(2') | 1.207(2) |

Table 3. Bond angles [°]

| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(7A)-N(1)-C(2) | 108.39(15) | C(3')-C(2')-N(1') | 110.38(15) |
| C(3)-C(2)-N(1) | 110.82(16) | C(2')-C(3')-C(3A') | 106.39(14) |
| C(2)-C(3)-C(3A) | 105.75(15) | C(2')-C(3')-C(8') | 127.01(15) |
| C(2)-C(3)-C(8) | 127.45(18) | C(3A')-C(3')-C(8') | 126.59(15) |
| C(3A)-C(3)-C(8) | 126.78(16) | C(4')-C(3A')-C(7A') | 119.12(15) |
| C(4)-C(3A)-C(7A) | 118.47(16) | C(4')-C(3A')-C(3') | 133.85(15) |
| C(4)-C(3A)-C(3) | 134.09(16) | C(7A')-C(3A')-C(3') | 107.02(14) |
| C(7A)-C(3A)-C(3) | 107.42(14) | C(5')-C(4')-C(3A') | 118.74(16) |
| C(5)-C(4)-C(3A) | 119.00(17) | C(4')-C(5')-C(6') | 121.30(17) |
| C(4)-C(5)-C(6) | 121.38(16) | C(7')-C(6')-C(5') | 121.27(16) |
| C(7)-C(6)-C(5) | 120.55(17) | C(6')-C(7')-C(7A') | 117.50(16) |
| C(6)-C(7)-C(7A) | 118.00(17) | N(1')-C(7A')-C(7') | 130.09(15) |
| N(1)-C(7A)-C(7) | 129.85(16) | N(1')-C(7A')-C(3A') | 107.86(14) |
| N(1)-C(7A)-C(3A) | 107.60(15) | C(7')-C(7A')-C(3A') | 122.06(15) |
| C(7)-C(7A)-C(3A) | 122.55(16) | C(3')-C(8')-C(9') | 111.09(13) |
| C(3)-C(8)-C(9) | 111.26(15) | N(2')-C(9')-C(8') | 112.47(13) |
| N(2)-C(9)-C(8) | 112.71(14) | C(10')-N(2')-C(17') | 111.90(13) |
| C(17)-N(2)-C(10) | 111.81(14) | C(10')-N(2')-C(9') | 123.23(14) |
| C(17)-N(2)-C(9) | 125.05(15) | C(17')-N(2')-C(9') | 124.83(14) |
| C(10)-N(2)-C(9) | 123.12(15) | O(1')-C(10')-N(2') | 124.54(15) |
| O(1)-C(10)-N(2) | 124.10(17) | O(1')-C(10')-C(11') | 129.02(16) |
| O(1)-C(10)-C(11) | 130.09(16) | N(2')-C(10')-C(11') | 106.43(14) |
| N(2)-C(10)-C(11) | 105.81(14) | C(12')-C(11')-C(16') | 122.00(15) |
| C(12)-C(11)-C(16) | 121.35(16) | C(12')-C(11')-C(10') | 129.91(16) |
| C(12)-C(11)-C(10) | 130.47(15) | C(16')-C(11')-C(10') | 108.08(14) |
| C(16)-C(11)-C(10) | 108.18(14) | C(11')-C(12')-C(13') | 116.89(18) |
| C(11)-C(12)-C(13) | 117.24(16) | C(14')-C(13')-C(12') | 120.87(18) |
| C(14)-C(13)-C(12) | 121.10(15) | C(13')-C(14')-C(15') | 121.80(17) |
| C(13)-C(14)-C(15) | 121.48(17) | C(16')-C(15')-C(14') | 116.97(18) |
| C(16)-C(15)-C(14) | 116.87(16) | C(15')-C(16')-C(11') | 121.46(16) |
| C(15)-C(16)-C(11) | 121.92(15) | C(15')-C(16')-C(17') | 130.30(17) |
| C(15)-C(16)-C(17) | 130.23(15) | C(11')-C(16')-C(17') | 108.24(14) |
| C(11)-C(16)-C(17) | 107.83(14) | O(2')-C(17')-N(2') | 124.79(16) |
| O(2)-C(17)-N(2) | 125.48(16) | O(2')-C(17')-C(16') | 129.88(16) |
| O(2)-C(17)-C(16) | 128.22(16) | N(2')-C(17')-C(16') | 105.33(14) |
| N(2)-C(17)-C(16) | 106.30(14) | | |
| C(7A')-N(1')-C(2') | 108.33(14) | | |

Table 4. Hydrogen bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(01)...O(2)#1 | 0.91(2) | 1.98(2) | 2.8369(19) | 156(2) |
| N(1')-H(01')...O(1')#2 | 0.90(2) | 2.06(2) | 2.9050(19) | 157(3) |
| C(8)-H(8B)...O(2')#3 | 0.99 | 2.59 | 3.325(2) | 130.9 |

# 6 Abbreviations

| | |
|---|---|
| 9-BBN | borabicyclo[3.3.1]nonane |
| Bp | boiling point |
| *m*CPBA | *meta*-chloroperbenzoic acid |
| DCM | dichloromethane |
| DIBAL-H | diisobutylaluminiumhydride |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| EI | electron ionization |
| ESI | *electrospray* ionization |
| HV | high vacuum |
| HMBC | heteronuclear multiple bond correlation |
| HPLC | high performance liquid chromatography |
| HSQC | heteronuclear single quantum correlation |
| HR | high resolution |
| IH | Isohexane |
| $IC_{50}$ | inhibitory concentration 50% |
| MCD | Magnetic Circular Dichroism |
| M.p. | melting point |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NMR | nuclear magnetic resonance |
| $R_f$ | retention factor |
| RP | reversed phase |
| rt | room temperature |
| TBAT | tetrabutylammonium difluorotriphenylsilicate |
| TBME | tert-Butyl methylether |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | tetramethylsilane |

# 7 Lebenslauf

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| | |
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